SYNTHESIS OF *O*-LINKED AMINO-CONDURITOL AND AMINO-INOSITOL DIMERS AND THEIR BIOLOGICAL PROPERTIES

By

JERREMEY WILLIS

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2002

To my family with all my love

ACKNOWLEDGEMENTS

First and foremost, I would like to thank God for the countless blessings that He has bestowed upon me and my family; without him none of this would be possible. I would like to thank my research advisor, Dr. Tomas Hudlicky, for his guidance, **patience** and friendship during my tenure at the University of Florida. His mentoring in chemistry, as well as a variety of other topics, has been greatly appreciated.

I would like to thank Dr. Josie Reed for her help with my written documents. Special thanks go to Dr. Reed also for keeping the boss happy and preventing him from seriously hurting any of his graduate students, namely me.

I would like to thank Dr. Dennis Wright for his contributions to my academic advancement. His door has always been open to me, and I really appreciate that.

I would like to thank the committee members, Dr. Merle Battiste, Dr. David Richardson, Dr. Dennis Wright, and Dr. Howard Johnson. Their support and encouragement have been outstanding. I would also like to thank the rest of the faculty in the Chemistry Department for sharing their extended knowledge.

I would like to extend special thanks to past and present members of Dr. Hudlicky's research group. Their encouragement and support have been priceless. Thanks go to Dr. Sherita D. McLamore, Dr. David Gonzalez, Dr. Bennett Novak, Dr. Mary Ann Endoma, and Dr. Nora Restrepo-Sanchez for answering countless questions on chemistry and how to deal with graduate school. Thanks go to Stanley Freeman and Dr.

Kofi Oppong, for their friendship and being there for me in good and bad times. I especially would like to thank Vu Phong Bui for the production of *cis*-diene diol; without him this research would not be possible.

On a more personal note, I would like to thank my family and friends. Their prayers, support, and understanding are greatly appreciated. Without their commitment to seeing my dreams come true, I would not be here today. To Mrs. Bethaney Willis, thank you for your endless support and devotion. I love you.

Thanks go to Virgil and Clemie Griffin, for watching over me from a boy to a man, and praying for me every step of the way. I admire them both and pray that I can raise my family half as well as they raised theirs. I thank Marilyn Clayborne, for working so hard and making a way for my sister and me. I appreciate all that she has done for me. I too know how hard it is to leave your own behind to make the future better for everyone. I thank Eddie Willis, for being there, and having a true and lasting impact on my life. I will always cherish our work days and the time we spent together. And to all my friends that I have lost along the way, **ONE LOVE**!

TABLE OF CONTENTS

page

ACKNOWLEDGMENTS iii

LIST OF ABBREVIATIONS vii

ABSTRACT x

CHAPTERS

1 INTRODUCTION 1

2 HISTORICAL 2

The Inositols 3
Introduction 3
Myo-Inositol 4
L-*Chiro* and D-*Chiro*-Inositol 6
Allo-Inositol 10
Neo-Inositol 16
Scyllo-Inositol 20
Epi-Inositol 21
Cis-Inositol 24
Muco-Inositol 27
The Conduritols 31
Introduction 31
Conduritol A 32
Conduritol B 39
Conduritol C 45
Conduritol D 52
Conduritol E 55
Conduritol F 59
Inositol Oligomers 64
Introduction 64
Synthesis of Cyclitol Oligomers 77
Molecular Properties 89
Inositol Signaling Pathways 91
The Inhibition of Glycosidases Hydrolases 94

3 DISCUSSION 98

The Synthesis of O-Linked Cyclitol Dimer 98
Introduction 98
Synthesis 99
Introduction 99
Retrosynthetic Analysis of the Target Molecule 99
Synthesis of Diene Diol 100
Synthesis of Vinyl Aziridine and Vinyl Epoxide 102
Nucleophilic Ring Opening of Epoxides and Aziridines 103
Failed Coupling Attempts 104
Synthesis of Inositol Dimer 1 106
Molecular Structure and Calcium Binding 114
Glycosidase Inhibition 116
Introduction 116
Results 116

4 AUXILARY REPORT 118

Introduction 118
Retrosynthetic Approach 119
Results 121

5 CONCLUSION 125

6 EXPERIMENTAL 127

APPENDICES 158

A SELECTED SPECTRA 158

B EXPERIMENTAL DATA 186

LIST OF REFERENCES 187

BIOGRAPHICAL SKETCH 196

LIST OF ABBREVIATIONS

acac	acetylacetonate
AD	asymmetric dihydroxylation
ADP	adenosine diphosphate
AIBN	azoisobutyronitrile
aq.	aqueous
ATP	adenosine trisphosphate
Bn	benzyl
Bz	benzoyl
CSA	camphor sulfonic acid
DBH	1,3-dibromo-5,5-dimethyl hydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethylazodicarboxylate
DAG	diacyl glycerol
DIAD	diisopropyl azodicarboxylate
DMAP	*N,N'*-dimethyl-4-amino pyridine
DMDP	2,5-dideoxy-2,5-diimino-D-mannitol
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide

ee	enantiomeric excess
ER	endoplasmatic reticulum
FVT	flash vacuum thermolysis
GDP	guanosine disposphate
GTP	guanosine trisposphate
HMPA	hexamethylphosphoric acid triamide
HPLC	high-performance liquid chromatography
IP_1	inositol-1-phosphate
IP_3	inositol trisphosphate
IPTG	iso-propyl-β-D-thiogalacto-pyranoside
KOH	potassium hydroxide
LAH	lithiumaluminum hydride
LDA	lithium diisopropylamide
*m*CPBA	*meta*-chloroperbenzoic acid
MOMCl	methoxymethyl chloride
MPLC	medium-pressure liquid chromatography
MsCl	methylsulfonyl chloride
NBS	*N*-bromosuccinimide
NMNO	*N*-methylmorpholine-*N*-oxide
PCC	pyridinium chlorochromate
PI	phosphatidylinositol
PIP_3	phosphatitylinositol 4,5-bisphosphate
PKC	protein kinase C

PLC	phospholipase C
p-NBA	*para*-nitrobenzoic acid
PNP	*para*-nitrophenyl
PPTS	pyridinium *para*-toulenesulfonic acid
Pr	propyl
pyr.	pyridine
RCM	ring-closing metathesis
RTK	receptor tyrosine kinase
SOBT	3-methyl-2-(selenoxo) benzothiazole
TBDPSCl	chloro-*tert*-butyldiphenylsilane
TBSCl	chloro-*tert*-butyldimethylsilane
TBTH	tributyl-tin hydride
TDII	*N,N'*-thiocarbonyldiimidazole
TEA	triethylorthoacetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TsCl	*para*-toluenesulfonyl chloride
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
VIS	visible

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

SYNTHESIS OF *O*-LINKED AMINO-CONDURITOL AND AMINO-INOSITOL DIMERS AND THEIR BIOLOGICAL PROPERTIES

By

Jerremey Willis

December 2002

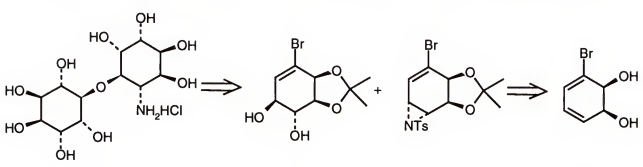
Chair: Tomas Hudlicky
Major Department: Chemistry

The synthesis of L-*chiro*-inositol-inositol dimer by chemical manipulation of the enantiomerically pure bromocyclohexadiene-*cis*-diol is described. Whole-cell biooxidation of bromobenzene with *Pseudomonas-putida* Escherichia *coli* JM109 (pDTG601) yields (1S,2S)-3-bromocyclohexa-3,5-diene-1,2-diol, which is protected as its acetonide and converted to vinyl oxirane and vinyl aziridine. One of the key steps in the synthesis of the unnatural saccharide is the nucleophilic opening of vinyl aziridine under Lewis acid conditions. Because of the inherent C_2 symmetry of the molecule, usage of a *trans*-diol, obtained by opening bromo-vinyl oxirane under basic conditions, allows access to the target via a convergent route.

CHAPTER 1
INTRODUCTION

Unnatural mono-and oligo-saccharides, in which the glycosidic oxygen or the endocyclic oxygen has been replaced by a methylene unit, have attracted a lot of attention from the synthetic community.[1] These compounds have shown a wide range of biological activity ranging from simple inhibition of glycosidic enzymes[2] to possible activity in cell adhesion and communication pathways.[3] Because such compounds lack the glycosidic linkage, they may be ideal candidates for screening as carbohydrate analogs for oral rather than intravenous application in cases where biological activities would mimic those of natural sugars.

The first portion of this dissertation describes the chemoenzymatic approach to an oxygen linked amino-inositol oligomer. Whole-cell fermentation of bromobenzene with



1 2 3 4

Figure 1 Retrosynthetic approach to target molecule

E. Coli JM109 (pDTG601) furnished a chiral *cis*-diene diol **4**, which was converted into its vinyl aziridine **3** and *trans*-diol **2**, respectively (Figure 1). Coupling of the two key

intermediates under Lewis acid conditions furnished an oxygen linked inositol conjugate, which was further manipulated to afford inositol-inositol dimer **1**.

The second part of this dissertation reports the chemistry I was involved in during the remainder of my residence at the University of Florida.

CHAPTER 2
HISTORICAL

The Inositols

Introduction

Inositols are hexahydroxycyclohexanes of which there are theoretically sixty four possible stereoisomers. However, there exist only nine actual compounds (Figure 2).

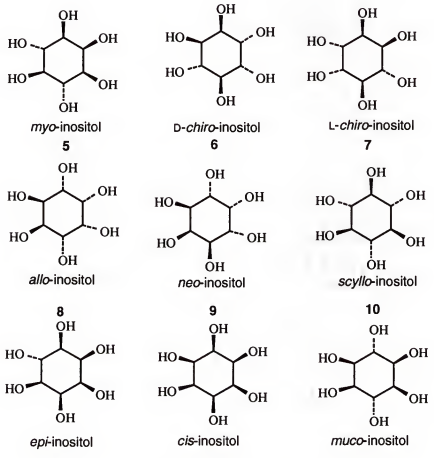


Figure 2 The nine inositols

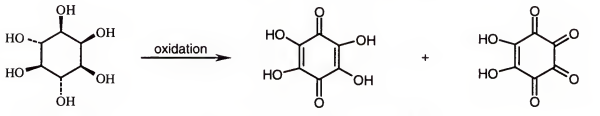
These cyclitols and their phosphate derivatives constitute an important class of compounds whose biological activities have been thoroughly reviewed.[4] Extensive work has gone into the synthesis of these cyclitols as well. Of the nine inositols listed in Figure 2, eight are commercially available. The least expensive is *myo*-inositol ($75/500g), and the most expensive being *scyllo*-inositol ($204/100 mg). Three of the inositol isomers, *myo*-, *scyllo*-, and *neo*-inositol, are found in nature, while the other diastereomers are usually synthesized from these compounds. Of all the cyclitols, *myo*-inositol has the widest occurrence. All plant or animal tissue examined thus far have been found to contain this substance.

A number of excellent reviews have been published concerning the inositols.[5] In the following sections, the synthesis of the nine inositols will be discussed.

Myo-Inositol

Scherer discovered *myo*-inositol in 1850.[6] Weiland and Wishart reported the first synthesis of myo-inositol over sixty years later.[7] Failed attempts to reproduce the work of Weiland and Wishart led to the re-investigation and a second synthesis of *myo*-inositol by Kuhn, Quadbeck, and Rohm in 1949.[8]

Maquenne did pioneering work towards structural elucidation.[9] By treating *myo*-inositol (**5**) with hydriodic acid, Maqueene was able to obtain quantities of benzene



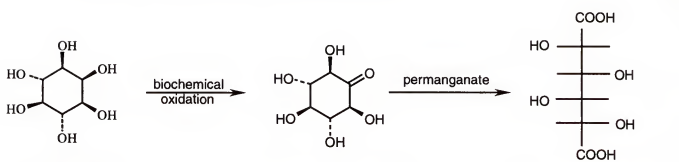
myo-inositol (**5**) Tetrahydroxy-*p*-benzoquinone (**14**) Rhodizonic acid (**15**)

Scheme 1

phenol, and triiodophenol. Tetrahydroxy-*p*-benzoquinone (**14**) and rhodizonic acid (**15**) were obtained upon oxidation of *myo*-inositol with concentrated nitric acid at 100°C (Scheme 1). From the data collected, Maquenne was able to conclude that he was working with a hexahydroxycyclohexane.

As with many compounds, the relative stereochemistry of *myo*-inositol was determined by its degradation and match to the structure of a compound whose stereochemistry was already assigned. In the early 1940's Posternak and Dangschat, via two different routes, helped to confirm the structure of *myo*-inositol.

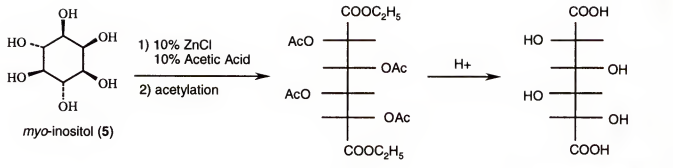
Posternak[10] studied *scyllo*-meso-inositol (**16**) (Scheme 2), which was obtained by Kluyver and Boezaardt[11] from the biochemical oxidation of *myo*-inositol. Oxidation of **16** with permanganate gave D,L-iodosaccharic acid (**17**).



myo-inositol (**5**) *scyllo*-meso-inositol (**16**) D,L-Idosaccharic acid (**17**)

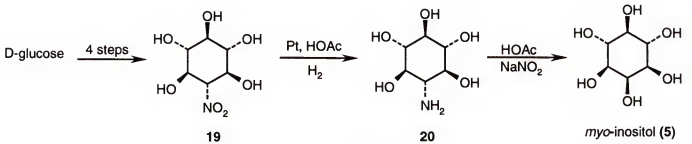
Scheme 2

Dangschat's structural proof of *myo*-inositol involved the tetraacetate derivative of D,L,-idosaccharate **18**.[12] By refluxing *myo*-inositol with excess acetone, 10% zinc chloride and 10% glacial acetic acid, followed by acetylation, Dangschat obtained compound **18** (Scheme 3), which upon deacetylation also afforded D,L-idosaccharic acid (**17**).



Scheme 3

Due to its relative abundance, very few synthetic approaches to *myo*-inositol have been published. In 1950 Posternak published the first total synthesis of *myo*-inositol (Scheme 4).[13]



Scheme 4

Amino-deoxy inositol **19** was obtained in four steps from D-glucose (Scheme 4). Reduction of the nitro group to the primary amine **20**, followed by hydrolysis under acidic conditions, gave *myo*-inositol.

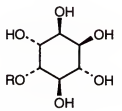
In 1983, one of the latest reported syntheses of *myo*-inositol from dianhydroinositols obtained from benzene was published by the Prinzbach group.[14]

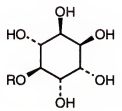
L-*Chiro* and D-*Chiro*-Inositol

In 1936, Posternak[15] reported the assignment of the absolute stereochemistry of both enantiomers of *chiro*-inositol. L-*Chiro*-inositol was obtained from quebrachitol (**21**)

by demethylation. Oxidation of the resulting product with $KMnO_4$ afforded mucic acid, whose absolute configuration was already known.

Quebrachitol (**21**) and pinitol (**22**) (shown in Figure 3) both afford easy access to both L-and D-*chiro*-inositol.



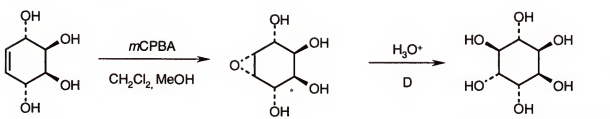


(**21**) R = CH_3 = Quebrachitol
(**7**) R = H = L-*chiro*

(**22**) R = CH_3 = (+)-Pinitol
(**6**) R = H = D-*chiro*

Figure 3 Structure of quebrachitol and pinitol

In 1992, Carless and co-workers prepared racemic *chiro*-inositol **25** from conduritol-A (**23**) (Scheme 5).[16]



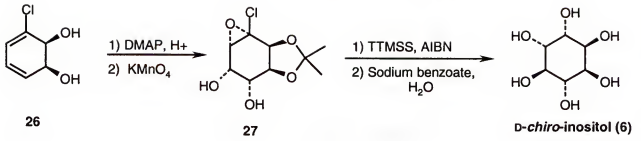
23 **24** (+/-)-*chiro*-inositol (**25**)

Scheme 5

Oxidation of **23** with peracid furnished epoxide **24** as a single isomer. Acid catalyzed ring opening of tetrol **24** produced (+/-)-*chiro*-inositol (**25**) in quantitative yield.

The first asymmetric synthesis of D-*chiro*-inositol was published in 1993 by Hudlicky and co-workers (Scheme 6).[17]

Beginning with *cis*-cyclohexadiene diol **26**, epoxide **27** was obtained by protecting the diol as its acetonide and oxidation with potassium permanganate.

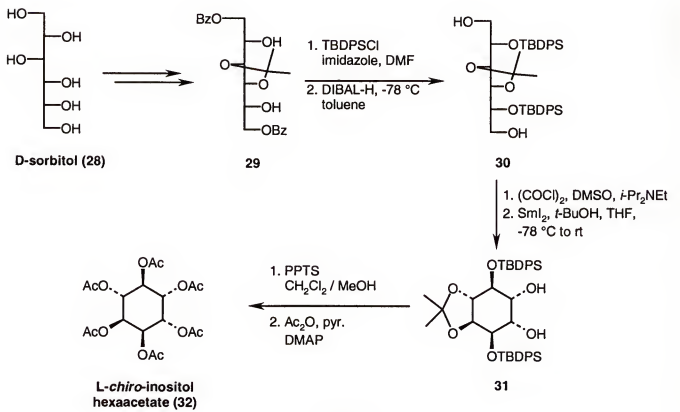


Scheme 6

Dehalogenation, epoxide opening and removal of the acetonide under acidic conditions gave D-*chiro*-inositol (**6**).

The Chiara group synthesized L-*chiro*-inositol **7** in 1995 (Scheme 7).[18]

D-Sorbitol (**28**) was selectively protected by a known procedure[19] to furnish diol **29**



Scheme 7

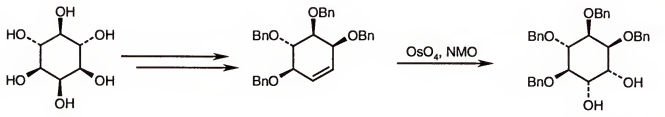
in 15% yield. Protection of the free hydroxy groups as their silyl ethers with TBDPSCl, followed by deprotection, afforded acetonide **30**. Incorporation of their earlier developed

one-pot sequence of Swern oxidation and SmI_2-promoted intramolecular pinacol[20] coupling afforded exclusively the L-*chiro* configured derivative **31** in 78% yield. Diol **31** was then deprotected to give L-*chiro*-inositol, which was characterized as its hexaacetate **32**.

Three years later, Kim and co-workers published a rather tedious approach to D-*chiro*-inositol.[21]

In 1999, Chung and Kwon synthesized a (+/-) *chiro*-inositol derivative from *myo*-inositol (Scheme 8).[22]

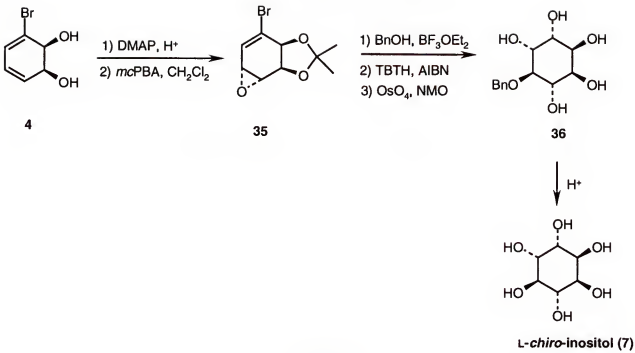
Myo-inositol was converted to tetrabenzoate **33** by a known procedure.[23] *cis*-Hydroxylation with osmium tetroxide furnished (+/-)-*chiro*-inositol derivative **34** in 95% yield.



***myo*-inositol (5)** **33** **(+/-)-*chiro*-inositol derivative 34**

Scheme 8

One of the more recent syntheses of L-*chiro*-inositol comes from the Hudlicky research group (Scheme 9).[24] Utilizing the general strategy developed earlier in their laboratories, Hudlicky and co-workers were able to synthesize L-*chiro*-inositol based on the peripheral oxygenation of the diene diol **4**. Epoxide **35**, obtained by the protection of diol **4** as its acetonide followed by epoxidation with *m*CPBA, was opened with benzyl alcohol under acid conditions. Dehalogenation, osmylation and subsequent removal of the acetonide with an ethanol/HCl mixture gave pentol **36**, which was coverted to L-*chiro*

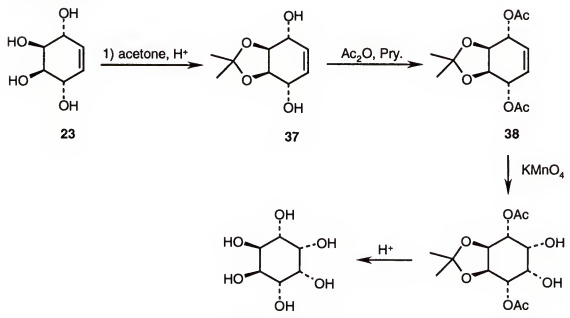


Scheme 9

inositol (**7**) by hydrogenation in 30% overall yield.

Allo-Inositol

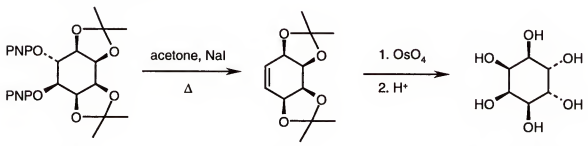
Dangschat and co-workers published the first synthesis of *allo*-inositol in 1939 (Scheme 10).[25]



Scheme 10

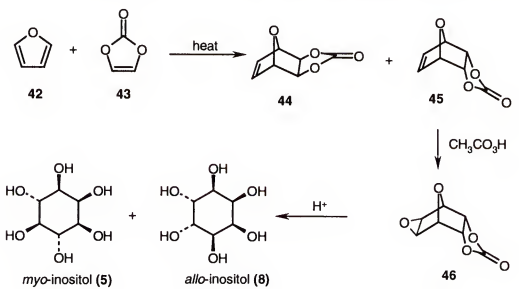
Treatment of conduritol-A (**23**), with acetone and 0.5% HCl, furnished acetonide **37** in 80% yield. Protection of diol **37** as the diacetate **38**, followed by *cis*-hydroxylation with 2% potassium permanganate yielded compound **39** in 8% yield. Deprotection of *cis*-diol gave *allo*-inositol (**8**).

In their efforts to synthesize *cis*-inositol (**12**), Angyal and Gilham also prepared *allo*-inositol (Scheme 11).[26]



Scheme 11

Beginning with bis-*O*-isopropylidene derivative **40**, elimination was achieved by refluxing the compound with sodium iodide to furnish the unsaturated bis-acetonide **41**. *cis*-Dihydroxylation of **41** and acid catalyzed deprotection furnished *allo*-inositol (**8**).

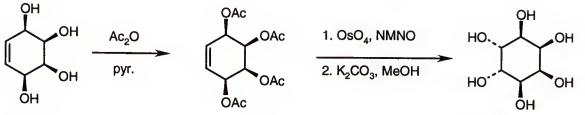


Scheme 12

In the 1970's, Kowarski and Sarel reported their preparation of *allo*-inositol (shown above in Scheme 12).[27]

Diels-Alder reaction of furan **42** with carbonate **43** at elevated temperatures gave a mixture of adducts **44** and **45** in 21% yield. Isomer **45** was epoxidized with peracetic acid to afford carbonate **46**. Acidic hydrolysis of **46** provided a mixture of *allo*-inositol and *myo*-inositol.

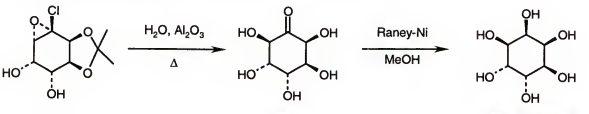
In 1992, Carless and co-workers published their synthesis of *allo*-inositol from conduritol-D (Scheme 13).[28]



Scheme 13

Tetraacetate **48** was obtained by treatment of conduritol-D (**47**) with acetic anhydride. Catalytic osmylation followed by hydrolysis of the acetates under basic conditions furnished *allo*-inositol (**8**) in 60% yield.

In the same year, the Hudlicky group used haloepoxide[29] **27** as starting material for their initial synthesis of *allo*-inositol (Scheme 14).[17]

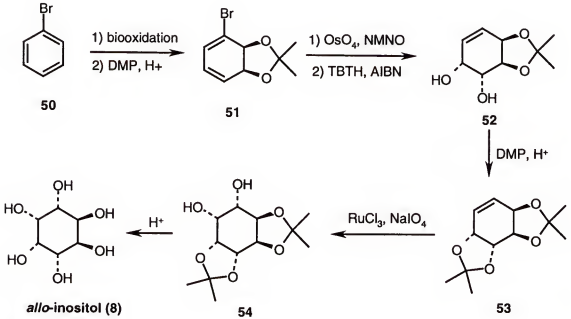


Scheme 14

Inose **49** was obtained from *cis*-diol **27** and sequentially reduced to provide *allo*-inositol (**8**).

Although other syntheses of *allo*-inositol have been reported, none allow for multigram scale-up. This problem was addressed by the Hudlicky group in 1997, when they reported a seven step synthesis of *allo*-inositol (Scheme 15).[30]

Enzymatic hydroxylation of bromobenzene (**50**) with *Escherichia coli* JM109 (pDTG601) afforded bromocyclohexadiene-*cis*-diol in a yield of 10g/L. Protection of this diol with 2,2-dimethoxypropane (DMP), acetone and a catalytic amount of *p*-toluenesulfonic acid furnished acetonide **51** in >98% yield. Osmylation of the unsubstituted diene, followed by reduction, gave alkene **52**. Protection of the *cis*-diol as

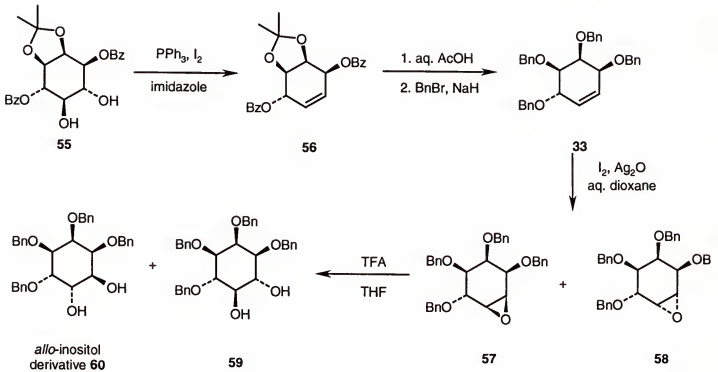


Scheme 15

its acetonide provided **53**. *cis*-Hydroxylation with sodium periodate and ruthenium (III) chloride afforded diol **54,** which upon deprotection with aqueous HCl in ethanol gave *allo*-inositol.

Chung and Kwon published the synthesis of a tetrabenzoate derivative of *allo*-inositol in 1999 (Scheme 16).[22]

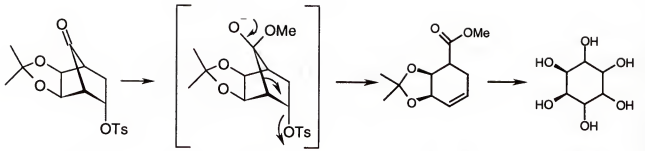
Known diol[31] **55**, was treated with triphenylphosphine, iodine, and imidazole to furnish acetonide **56** in 77% yield. Deprotection followed by benzylation gave alkene **33**. Epoxidation with iodine in aqueous dioxane furnished a mixture of epoxides **57** and **58** in 89% yield. Solvolysis of the separated epoxides under acidic conditions furnished a



Scheme 16

mixture of *allo*- and *myo*-inositol benzoates in 65% and 16% yield respectively.

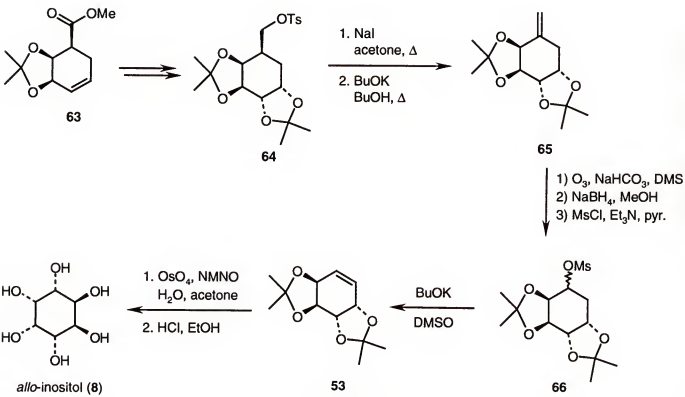
One of the more recently published syntheses of *allo*-inositol came via work by the Mehta research group.[32] Taking advantage of the grob-like fragmentation sequence



61 62 63 64

Figure 4 Grob-like fragmentation mechanism

in norobornyl derivative **61**, Mehta constructed methylester intermediate **63** which was used for the synthesis of polyoxygenate cyclohexenoids **64** (Figure 4).



63 64 65 66 53 *allo*-inositol (8)

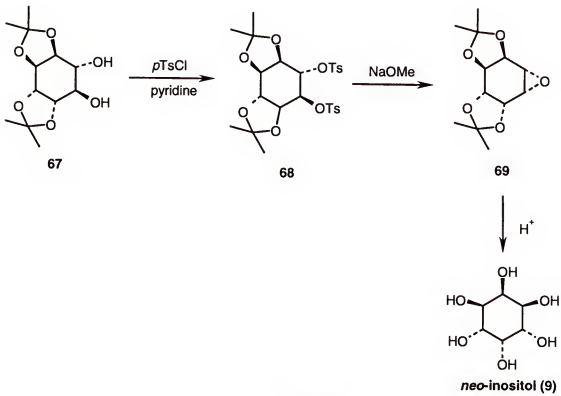
Scheme 17

Ester **63** was converted, in a few steps, to tosylate **64**, which upon elimination with sodium iodide afforded olefin **65** (Scheme 17). Mesylate **66** was obtained via ozonolysis, followed by reduction and mesylation. Base mediated elimination provided

access to alkene **53**. Catalytic osmylation followed by deprotection furnished *allo*-inositol **(8)**.

Neo-Inositol

In 1955, the first successful synthesis of *neo*-inositol was accomplished by Angyal and Matheson in a two-step synthesis from 1,2:5,6-di-O-isopropylidine-L-*chiro*-inositol (**67**) (Scheme 18).[33]

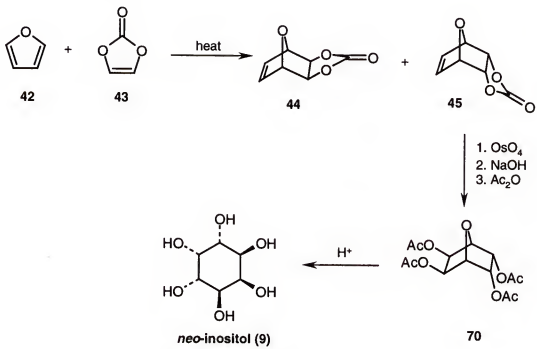


Scheme 18

Ditosylation of **67** with *p*-toluenesulfonyl chloride in pyridine afforded the fully protected cyclitol **68**. Treatment of the ditosylated compound with sodium methoxide yielded epoxide **69**. When this epoxide was heated with dilute sulfuric acid, *neo*-inositol (**9**) was formed. Although the structural proof was not offered, the fact that it was not

identical to any of the other six known inositol diastereomers led Angyal and Matheson to conclude that a new inositol had been synthesized.

Kowarski and Sarel prepared *neo*-inositol in a similar fashion as described for *allo*-inositol (Scheme 19).[27]

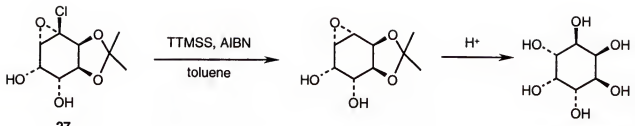


Scheme 19

Diels alder adduct **45** was *cis*-hydroxylated with osmium tetroxide and protected as its tetraacetate ether to furnish **70**. Acidic hydrolysis of **70** provided *neo*-inositol (**9**) in quantitative yield.

In 1992, the Hudlicky group synthesized *neo*-inositol using haloepoxide **27** as starting material (Scheme 20).[17]

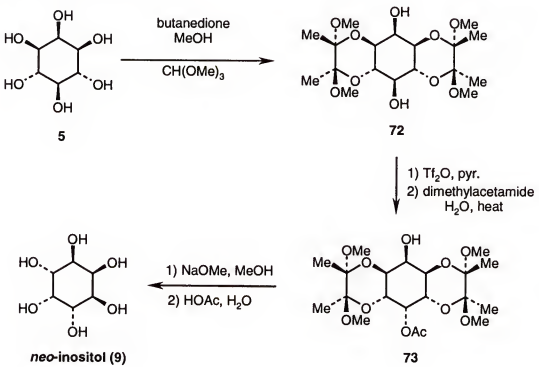
Dechlorination of **27** under radical conditions provided epoxide **71**. Acidic



Scheme 20

hydrolysis furnished *neo*-inositol (**9**) in 50% yield.

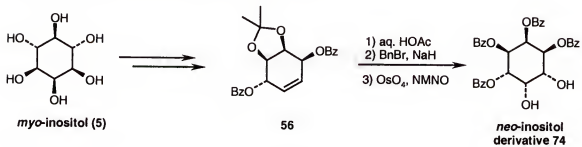
Starting from *myo*-inositol, Potter and co-workers achieved the synthesis of *neo*-inositol in 1998 (Scheme 21).[34]



Scheme 21

Selective protection of the *trans*-diol moieties gave diol **72** in 27% yield. Triflation and sequential replacement of the resulting ether by acetate, in an S_N2-type fashion, afforded alcohol **73**. Removal of all protecting groups furnished *neo*-inositol (**9**) in 60% yield over two steps.

One year later, Chung and Kwon reported the synthesis of a *neo*-inositol derivative starting with *myo*-inositol (Scheme 22).[22]

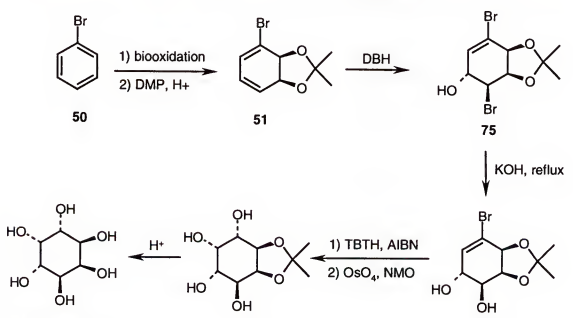


Scheme 22

According to a known procedure,[31] *myo*-inositol was converted to dibenzoate **56**. Deprotection followed by benzylation and oxidation of the alkene afforded *neo*-configured inositol derivative **74** in 77% yield.

In a more recent synthesis, Hudlicky and co-workers prepared *neo*-inositol from bromobenzene (Scheme 23).[35]

Biooxidation of bromobenzene (**50**) followed by protection afforded acetonide **51**.

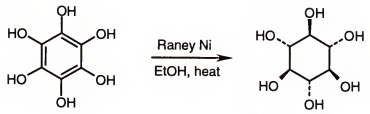


Scheme 23

Treatment of **51** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in acetone-water yielded bromohydrin **75**. *Trans*-diol **76** was obtained by treating bromohydrin **75** with excess aqueous KOH at elevated temperatures to facilitate hydrolysis. Radical debromination of **76**, followed by oxidation with OsO_4, yielded tetrol **77**. Removal of the acetonides with methanolic HCl provided *neo*-inositol in 77% yield.

Scyllo-Inositol

Scyllo-inositol, another of the naturally occurring inositols, was discovered in 1858.[36] It was not until the work by Posternak[37] in 1942, during his investigation of the configuration of *myo*-inositol, that the stereochemical configuration was confirmed.

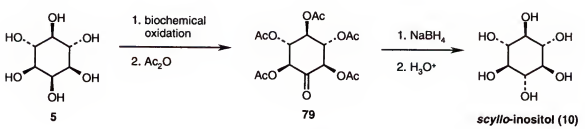


78 **scyllo-inositol (10)**

Scheme 24

The first synthesis of *scyllo*-inositol was published by Anderson and Wallis[38] in 1948. Reduction of hexahydroxycyclobenzene **78** with Raney Ni afforded *scyllo*-inositol (**10**) in moderate yields as depicted in Scheme 24.

In 1985, Kohne and Praefcke prepared *scyllo*-inositol, starting from *myo*-inositol (Scheme 25).[39]



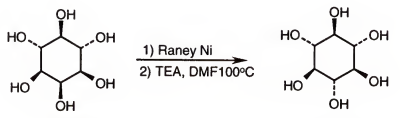
5 **79** **scyllo-inositol (10)**

Scheme 25

Biooxidation of *myo*-inositol (**5**) with *Acetobacter suboxydans*,[40] followed by acetylation, afforded pentaacetate **79**. Inose **79** was reduced with sodium borohydride and the resulting alcohol deprotected to give *scyll*o-inositol (**10**) in 69-78% yield.

A *scyllo*-configured cyclitol was also obtained as a byproduct in Chung and Kwons's synthesis of (+/-)-*chiro*-inositol.[22]

In 1998, Vottero and co-workers designed a new set of conditions to isolate *scyllo*-inositol from the orthoacetate derivative of *myo*-inositol (Scheme 26).[41]



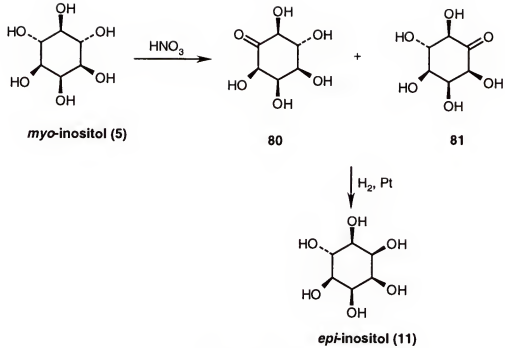
myo-inositol **(5)** *scyllo*-inositol **(10)**

Scheme 26

Taking advantage of *scyllo*-inositol's low-solubility in H_2O and the higher solubility of *myo*-inositol orthoacetate in the same solvent, Vottero *et al.* dissolved *myo*-inositol (**5**) in distilled H_2O and refluxed with Raney Nickel. After workup the crude mixture of inositols were dissolved in DMF and stirred with triethylorthoacetate in the presence of *p*-toluenesulfonic acid. After 18 hours the solvent was removed and the residue redissolved in hot water. *Scyllo*-inositol (**10**) was obtained as a white crystalline mass in about 80% yield.

Epi-Inositol

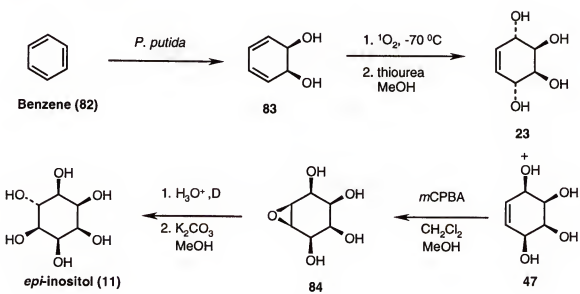
Posternak is credited with the first synthesis of *epi*-inositol,[42] although, at the time, he was unaware of the configuration of the new cyclitol formed. He revisited this work some five years later[43] and was able to prove the stereochemistry by oxidizing *myo*-



Scheme 27

inositol to a mixture of two inososes **80** and **81**. Hydrogenolysis gave *epi*-inositol (**11**) as shown in Scheme 27.

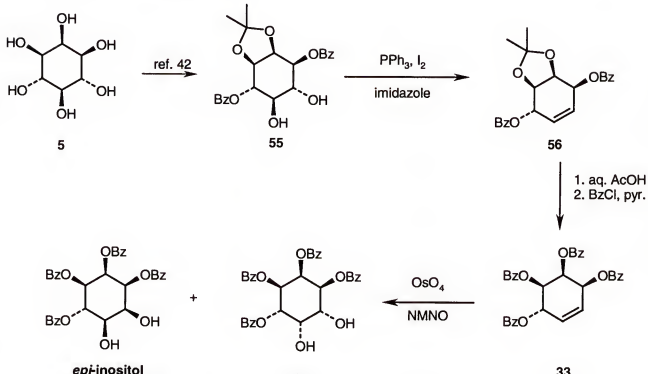
In 1992, Carless and co-workers synthesized *epi*-inositol using a chemoenzymatic approach (Scheme 28).[44]



Scheme 28

Microbial oxidation of benzene with *Pseudomonas putida* afforded *cis*-diol **83**. Photo-oxygenation of **83** furnished a mixture of endoperoxides, which were separated and converted by acid-catalyzed ring-opening to conduritol-A (**23**) and conduritol-D (**47**), respectively. Epoxidation of conduritol-D with *m*CPBA furnished epoxide **84**. Acid-catalyzed ring-opening of **84** gave *epi*-inositol in 79% yield.

Chung and Kwon published the synthesis of a protected derivative of *epi*-inositol in 1999 (Scheme 29).[22]

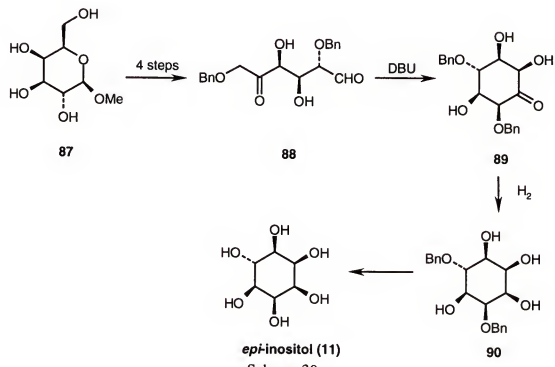


Scheme 29

Myo-inositol was converted to *trans*-diol **55.** Treatment of diol **55** with triphenylphosphine, imidazole and iodine gave cyclohexene derivative **56** in 77% yield. Removal of the acetonides followed by benzoylation furnished tetrabenzoate **33** in 91% yield. Oxidation of the double bond with osmium tetroxide gave a mixture of *neo*- and *epi*-inositol configured products in 42% and 31% yield, respectively.

In 2000, Catelani and Carsaro reported the synthesis of *epi*-inositol from commercially available methyl β-D-galactopyranoside (Scheme 30).[45]

Following a previously described synthetic route[46] pyranoside **87** was converted to aldehyde **88**. Treatment of **88** with DBU at room temperature gave triol **89** in 60%

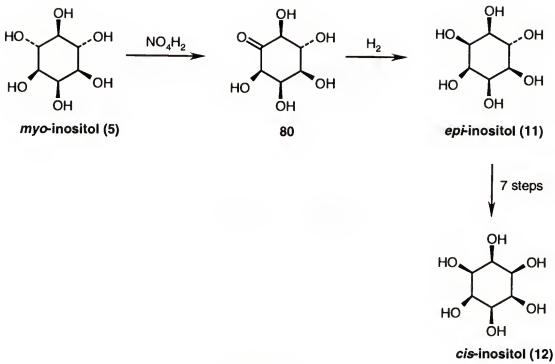


Scheme 30

yield. Inose **89** was then selectively reduced by catalytic hydrogenation to give tetrol **90**. *Epi*-inositol (**11**) was obtained in nearly quantitative yields by catalytic debenzylation.

Cis-Inositol

Cis-inositol was first isolated as one of several products formed in the high-pressure hydrogenation of tetrahydroxyquinone over Raney Nickel.[47] The first synthesis of *cis*-inositol was published in 1971 by Angyal and Hickman (Scheme 31).[48]

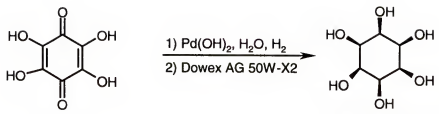


Scheme 31

Beginning with *epi*-inositol, these chemists were able to complete their synthesis in seven steps in an overall yield of 25%. Although the synthesis was a success and completed in relatively few steps, one drawback in this approach was the construction of the key intermediate, *epi*-inositol.

Epi-inositol (**11**) was obtained by the oxidation of commercially available *myo*-inositol (**5**) with nitric acid to give 2,3,4,6/5-pentahydroxycyclohexanone (**80**), which upon catalytic hydrogenation, gave the aforementioned compound in only 10-15% yield. The preparation of **11** was more arduous and time consuming than the subsequent steps involved in the synthesis of *cis*-inositol.

Almost a quarter of a century later, Angyal revisited this project and in 1995 published a "simple" synthesis of *cis*-inositol (Scheme 32).[49] Utilizing ion-exchange chromatography as a method of purification and improving on the hydrogenation



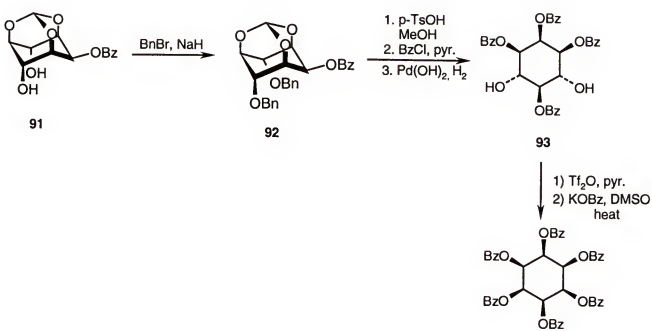
14 ***cis*-inositol (12)**

Scheme 32

procedure developed by Anderson and Wallis,[33] *cis*-inositol was obtained by reduction of tetrahydroxyquinone (**14**) and isolated in 31% yield.

In 1999, Chung and Kwon published the most recent synthesis of *cis*-inositol (Scheme 33).[22]

2-O-Benzyl-*myo*-inositol orthoformate (**91**) obtained from *myo*-inositol by a known procedure,[50] was treated with benzyl bromide under basic conditions to give **92** in



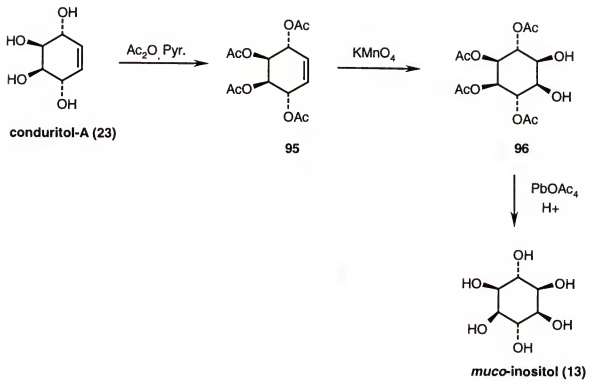
91 **92** **93** **94**

Scheme 33

82% yield. Successive hydrolysis of the orthoformate, benzoylation, and hydrogenolysis of the resulting benzyl ethers gave diol **93**. Triflation followed by S_N2 type exchange when heating **93** with KOBz in DMSO gave the hexabenzoate *cis*-inositol conjugate **94** in overall good yield.

Muco-Inositol

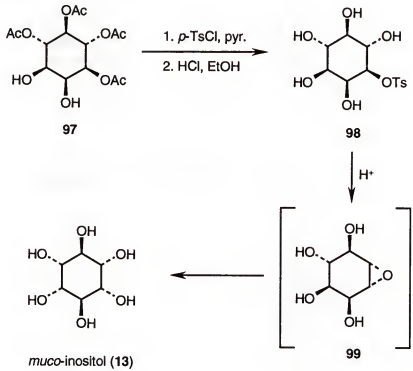
Muco-inostiol's first synthesis was also achieved by Dangschat and Fischer in 1939 in a similar manner to that of *allo*-inositol (Scheme 34).[25] Acetylation of



Scheme 34

conduritol-A (**23**) with acetic anhydride and pyridine, furnished tetraacetate **95**. *Cis*-dihydroxylation with 1 mol of potassium permanganate yielded diol **96** in 60% yield. Deprotection provided *muco*-inositol (**13**).

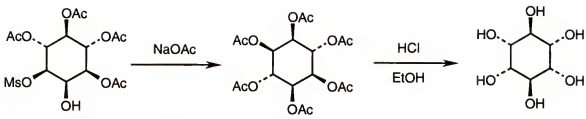
In 1966, Angyal *et al.* published the synthesis of *muco*-inositol from a tetraacetate *myo*-inositol derivative (Scheme 35).[51]



Scheme 35

1,4,5,6-tetra-*O*-acetyl-*myo*-inositol (**97**) was transformed to tosyl derivative **98** under standard conditions, taking advantage of an intramolecular acetyl migration. Treatment of **98** with a basic ion-exchange resin gave epoxide **99** as an intermediate, which under the reaction conditions underwent *trans*-diaxial ring opening to furnish *muco*-inositol (**13**).

The following year, Lichtenthaler and co-workers were able to prepare *muco*-inositol from another *myo*-inositol derivative as shown in Scheme 36.[52]



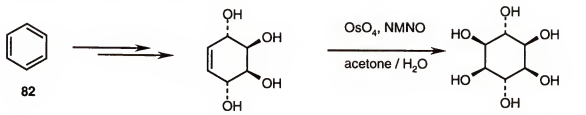
100 **101** *muco*-inositol (**13**)

Scheme 36

Treatment of known[53] methanesulfonyl ester **100** with sodium acetate provided *muco*-inositol hexacetate **101** by intermolecular rearrangement by an acetyloxonium ion. *Muco*-inositol (**13**) was obtained by acidic hydrolysis of compound **101**.

In 1980, Angyl published a second synthesis of *muco*-inositol starting from a quebrachitol derivative.[54]

In 1992, the Carless group synthesized *muco*-inositol from the chemoenzymatic oxidation of benzene (Scheme 37).[28]



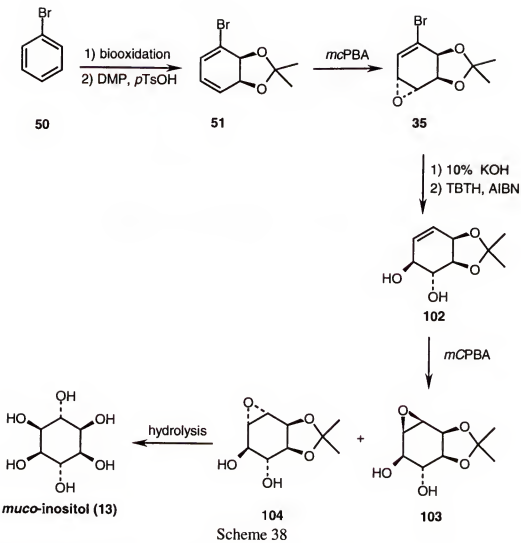
82 **23** *muco*-inositol (**13**)

Scheme 37

Previously reported conduritol-A was oxidized with OsO_4 yielding *muco*-inositol in 82% yield.

In 1993, the Hudlicky group published their first synthesis of *muco*-inositol.[55] Five years later their group improved upon this approach and reported their second synthesis of *muco*-inositol in six steps and 45% overall yield (Scheme 38).[56]

Microbial oxidation of bromobenzene (**50**) followed by protection of the resulting

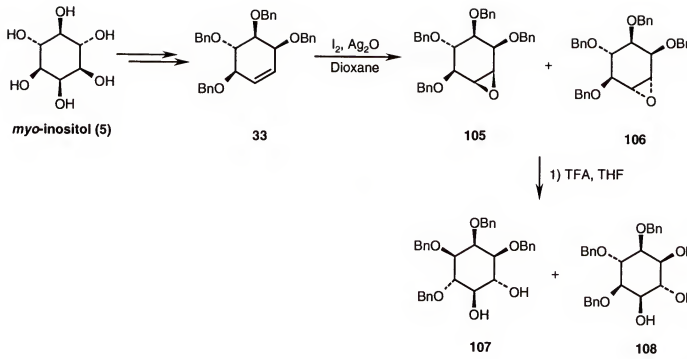


Scheme 38

diol as its acetonide afforded diene **51**. Epoxidation with *m*CPBA gave epoxide **35**. Regio and stereoselective opening of **35**, with 10% aqueous KOH, followed by debromination gave *trans*-diol **102**. Epoxidation of the alkene provided a mixture of α and β epoxides in a ratio of 1:1.8 (**103:104**) in 71% yield. Hydrolysis of the mixture of epoxides, followed by deprotection gave *muco*-inositol (**13**) in 75% yield.

In 1999, Chung and Kwon published the synthesis of *muco*-inositol tetrabenzoyl derivative **33** starting from *myo*-inositol as illustrated in the Scheme 39.[22]

Myo-inositol was transformed to tetrabenzoate **33**. Oxidation of the



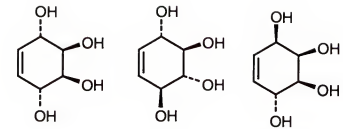
Scheme 39

double bond gave a mixture of epoxides **105** and **106** in 86% overall yield. Hydrolysis of epoxide **106** gave the desired *muco*-inositol **108** analog in 64% yield.

The Conduritols

Introduction

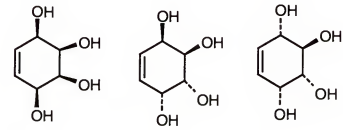
In 1908, Kubler,[57] isolated conduritol-A from the bark of the vine *Marsdenia condurango*. Dangschat and Fischer elucidated the structure and configuration of this compound 30 years later.[58] All six conduritols shown in Figure 5 below have been synthesized by many different synthetic sequences. The following sections will consist of the syntheses of each conduritol.



23 conduritol-A

109 conduritol-B

110 conduritol-C



47 conduritol-D

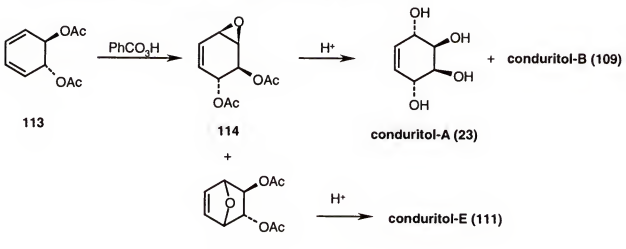
111 conduritol-E

112 conduritol-F

Figure 5. The six Conduritols

Conduritol-A

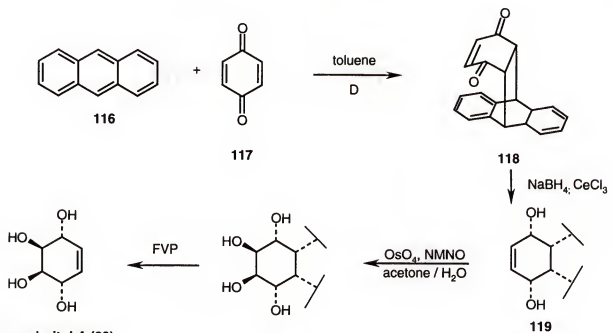
In 1957, Nakajima and co-workers published the synthesis of three conduritol isomers, one of which was conduritol-A (Scheme 40).[59]



Scheme 40

Oxidiaton of the diacetate **113** with peracid gave a mixture of cyclic alkenes **114** and **115**. Hydrolysis afforded a mixture of conduritol isomers. Although two of the conduritols had all ready been synthesized, this marked the first synthesis of conduritol-A (**23**).

Knapp and co-workers reported the first stereospecific synthesis of conduritol-A

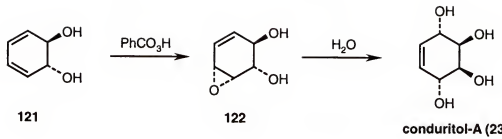


Scheme 41

in 1983.[60] Three years later the Rutledge research group improved on Knapp's work and reported an abbreviated route to conduritol-A (Scheme 41).[61]

Diels-Alder adduct **118** (obtained in 86% yield) was reduced under Luche conditions to give diol **119** in 97% yield. Dihydroxylation of **119** furnished tetrol **120**. The latter gave conduritol-A (**23**) upon flash vacuum pyrolysis in quantitative yield.

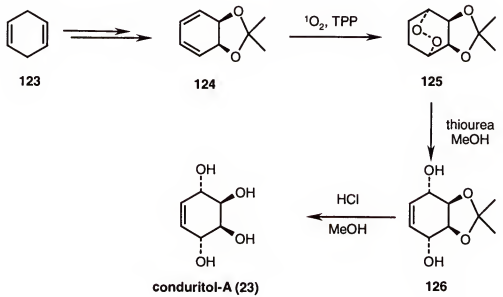
In 1985, Aleksejezyk and Berchtold prepared conduritol-A starting from *trans*-diol **121** (Scheme 42).[62]



Scheme 42. The synthesis of conduritol-A by Aleksejezyk and Berchtold

Diene-diol **121** was converted to conduritol-A (**23**) by epoxidation and subsequent hydrolysis.

The Balci research group reported another synthesis of conduritol-A, starting from 1,4-cyclohexadiene in the late eighties (Scheme 43).[63]



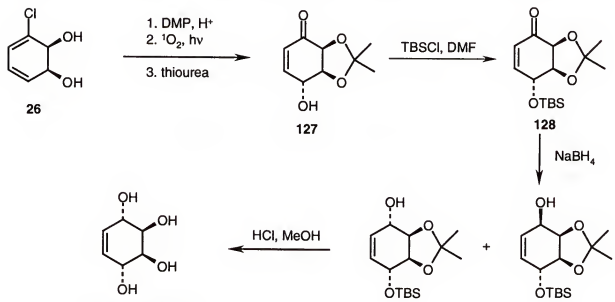
Scheme 43. Balci's synthesis of conduritol-A

Diene **123** was converted to protected diol **124** by a known procedure.[64] Photo-oxygenation of **124** furnished endoperoxide **125** (95%), which was reduced to give **126**. Deprotection furnished conduritol-A (**23**) in quantitative yield.

Three years after Balci's report was published, the Hudlicky group achieved the

construction of conduritol-A via a chemoenzymatic approach (Scheme 44).[65]

Protection of diol **26** as an acetonide, followed by singlet-oxygen addition and cleavage of the peroxide-bond with thiourea furnished enone **127** in 88% overall yield.



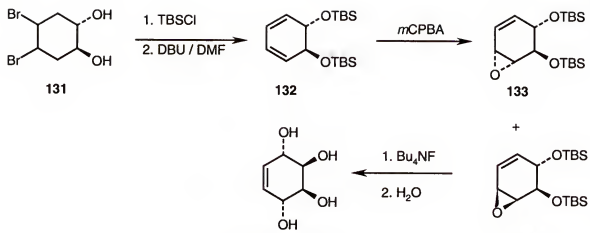
Scheme 44. The synthesis of conduritol-A by Hudlicky *et al.*

TBS-protection of the alcohol in **127** yielded ether **128** in 85% yield. Reduction of the ketone functionality with sodium borohydride gave a 1:1 mixture of alcohols **129** and **130**, respectively. Isomer **130** furnished conduritol-A upon acidic hydrolysis.[66]

Conduritol-A was also prepared by Carless and Oak as a side product during their approach towards conduritol-D.[67]

In 1994, Billington and co-workers reported the synthesis of several conduritol isomers, one of them being conduritol-A (Scheme 45).[68]

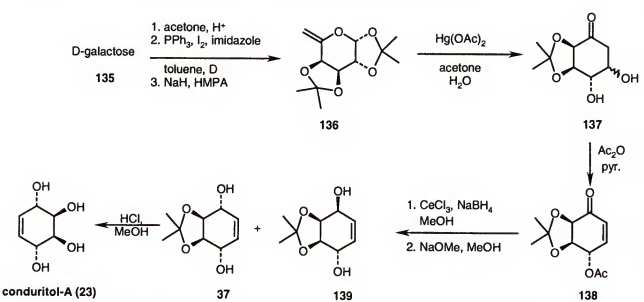
Protection of known[69] dibromodiol **131** as its *bis*-TBS ether followed by elimination provided diene **132**. *m*CPBA epoxidation of diene **132** gave a 1:1 mixture of



Scheme 45

epoxides **133** and **134** which were separated by chromatography. Removal of the TBS group with tetrabutylammonium fluoride and hydrolysis of epoxide **134** furnished conduritol-A.

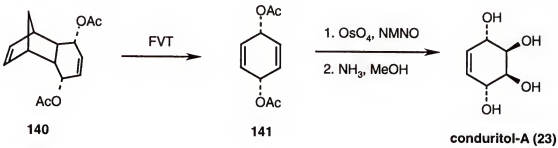
D-Galactose, obtained from a chiral pool, was used as the starting material by Mereyala and Gaddam who prepared conduritol-A in 1994 (Scheme 46).[70]



Scheme 46. The synthesis of conduritol-A by Mereyala and Gaddam

In three steps, D-Galactose (135) was converted to enone 136 in 74% yield. Alkene **136** was then subjected to the conditions of the Ferrier-rearrangement,[71] producing cyclohexanone derivative **137** in 83% yield. Elimination followed by protection gave enone **138**. Reduction of the enone and removal of the acetate afforded the two diols **37** and **139** (69% overall yield), which could be separated by chromatography. Removal of the acetonide in compound **37** furnished conduritol-A (**23**) in quantitative yield.

In 1995, Zwanenburg *et al.* used a cycloaddition approach to conduritol-A, (Scheme 47).[72]



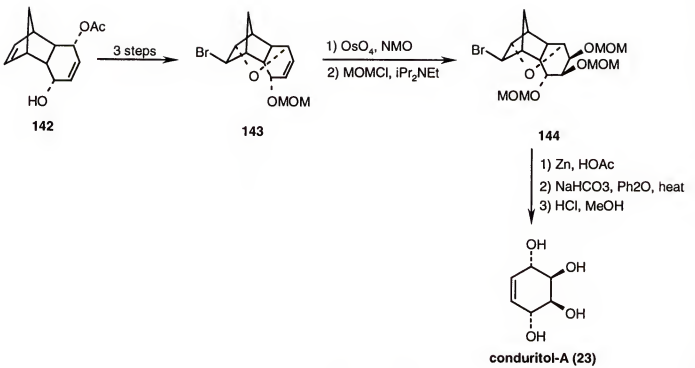
140 **141** **conduritol-A (23)**

Scheme 47. Zwanenburg's approach to conduritol-A

Diels-Alder adduct **140** was subjected to flash vacuum thermolysis to furnish diacetate **141**. Hydroxylation of one of the alkenes in **141**, followed by deprotection under basic conditions furnished conduritol-A.

Ogasawara and co-workers published the first convergent synthesis of all six conduritols starting from a single chiral compound in 1999 (Scheme 48).[73]

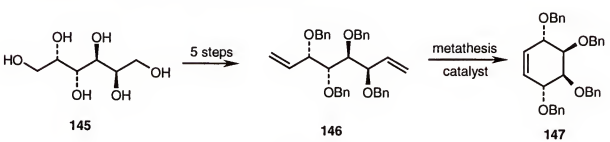
Acetate **142** was transformed in three steps to bromo-ether **143** to discriminate one the of two olefin functionalities. Dihydroxylation followed by protection gave the



Scheme 48

tri-MOM ether **144** in nearly quantitative yield. Conduritol-A was obtained from **144**, via sequential reductive cleavage, thermolysis, and MOM deprotection.

In a more recent synthesis,[74] Furstner and co-workers synthesized conduritol-A via a ring-closing metathesis reaction (Scheme 49).

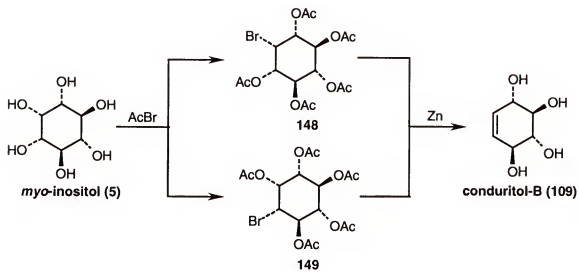


Scheme 49

Diene **146,** obtained in five steps from **145** underwent ring-closing metathesis using either the ruthenium catalyst developed by Grubbs[75] or with Schrock's molybdenum catalyst[76] affording tetra-*O*-benzyl conduritol-A **147** in greater than 90% yield.

Conduritol-B

Building on the work reported by Muller in 1907,[77] McCasland published the synthesis of conduritol-B in 1953 (Scheme 50).[78] Muller had observed that treatment of pentaacetate **148** or **149** with Zn, in the presence of acetic acid, gave a product that

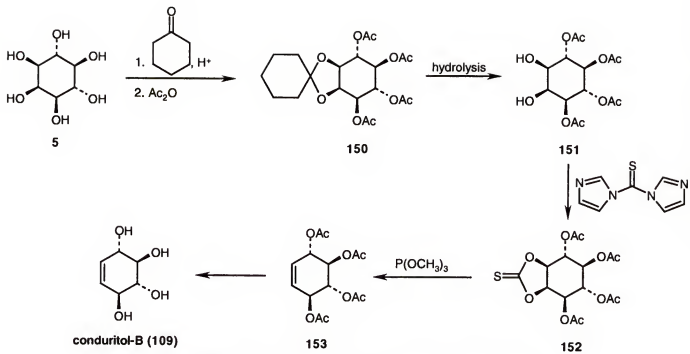


Scheme 50

analyzed as $C_{14}H_{18}O_6$. McCasland repeated these steps and, upon deacylation of the Muller intermediate, obtained conduritol-B.

In 1970, starting from *myo*-inositol, Nagabhushan reported the synthesis of conduritol-B (Scheme 51).[79]

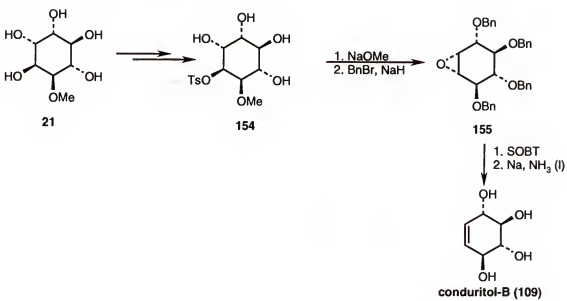
Myo-inositol was converted to its cyclohexylidene ketal, followed by acetylation of the hydroxyl groups to give tetraacetate **150**.[80] Hydrolysis of ketal **150** gave diol **151**, which was converted to its thiocarbonate **152** in 40% yield. Deoxygenation under Corey-Winter conditions was performed using trimethyl phosphite to provide alkene **153**.



Scheme 51. Nagabhushan's synthesis of conduritol-B

Removal of the acetate functionality under acidic conditions furnished conduritol-B (**109**) in 74% yield.

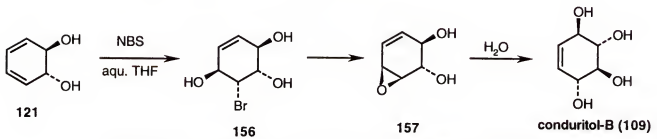
The first enantioselective synthesis of conduritol-B was reported in 1981 by Paulsen *et al.* and is shown in Scheme 52.[81]



Scheme 52

Quebrachitol (**21**) was converted to tetrol **154**, which after treatment with sodium methoxide and subsequent benzylation furnished epoxide **155** in 88% yield. Reductive deoxygenation of **155** with 3-methyl-2-(selenoxo) benzothiazole (SOBT)[82] followed by removal of the benzyl protecting groups furnished conduritol-B (**109**) in 55% yield.

Aleksejezyk and Berchtold synthesized conduritol-B using the same methodology employed in their synthesis of conduritol-A (Scheme 53).[62]

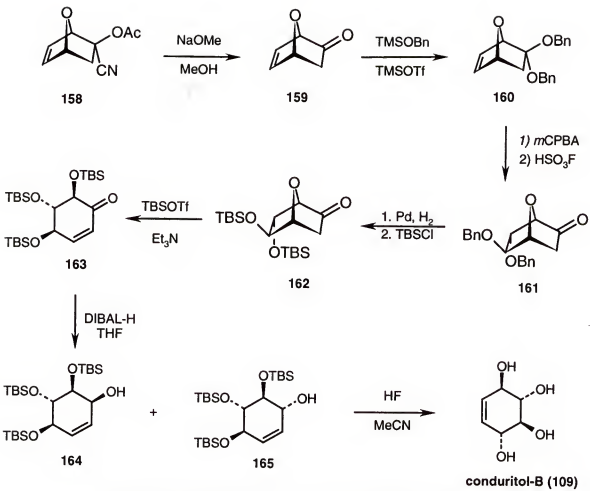


Scheme 53. The synthesis of conduritol-B by Aleksejezyk and Berchtold

Trans-Diol **121** was brominated under radical conditions with NBS to furnish bromohydrin **156**. Epoxidation furnished **157**, which upon hydrolysis gave conduritol-B (**109**).

In 1990, the Vogel group published their synthesis of conduritol-B starting from bicyclic nitrile **158** (Scheme 54).[83]

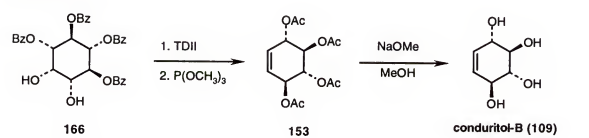
Saponification of nitrile **158** with base followed by treatment with formalin furnished ketone **159** in 93% yield. Alkene **159** was converted to dibenzyl ketal **160** using a method developed in the Noyori group.[84] Epoxidation of **160** followed by ring opening with fluorosulfonic acid and protection of the resulting diol as the benzyl ethers gave **161**. Cleavage of the latter by hydrogenolysis and re-protection of the alcohols as silyl ethers, gave ketone **162** in greater than 90% yield. The bicyclic system was cleaved with TBSOTf to furnish enone **163**. DIBAL-H reduction of enone **163** gave a 1:5 mixture



Scheme 54. The synthesis of conduritol-B by the Vogel group

of alcohols **164** and **165**, respectively. Treatment of isomer **165** with HF furnished conduritol-B (**110**) in 86% yield.

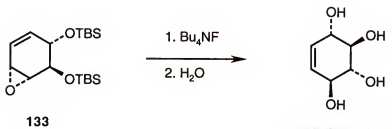
In 1991, the Akiyama group reported the first synthesis of (+)-conduritol-B (Scheme 55).[85]



Scheme 55. Akiyama's synthesis of (+)-conduritol-B

Tetrabenzoate **166**, which they had prepared earlier for a different project,[86] was subjected to Corey-Winter conditions providing alkene **153** in 88% yield over two step. Hydrolysis of the ester furnished conduritol-B in quantitative yield.

Conduritol-B was prepared by Billington and co-workers as well in 1994 (Scheme 56).[68]



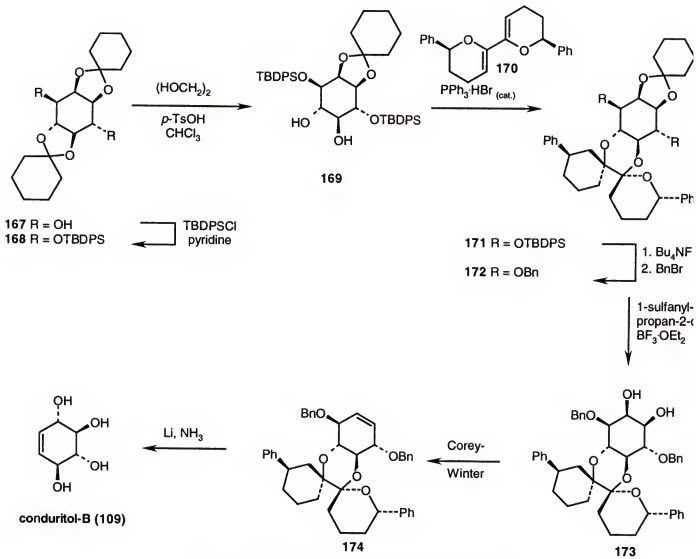
133 **conduritol-B (109)**

Scheme 56. Billington's synthesis of conduritol-B

Epoxide **133**, obtained as a by-product in their synthesis of conduritol-A was deprotected in the presence of fluoride and subjected to aqueous hydrolysis to furnish conduritol-B.

Yet another preparation of conduritol-B was reported by Ley and co-workers in 1997, starting from a derivative of *myo*-inositol (Scheme 57).[87]

Protection of the free hydroxyl groups in 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**167**), which is available from *myo*-inositol in one step, afforded TBDPS-ether **168** in 72% yield. Selective cleavage of one of the acetals furnished *trans*-diol **169**. A one pot protection/resolution reaction with (2*S*, 2'*S*)-2,2'-diphenyl-6,6'-bi(3,4-dihydro-2*H*-pyran) (**170**) allowed access to chiral species **171** in 35% yield. Exchange of protecting groups from TBDPS to benzyl (**172**) followed by cleavage of the cyclohexylidene acetal gave diol **173** in quantitative yield. Corey-Winter deoxygenation

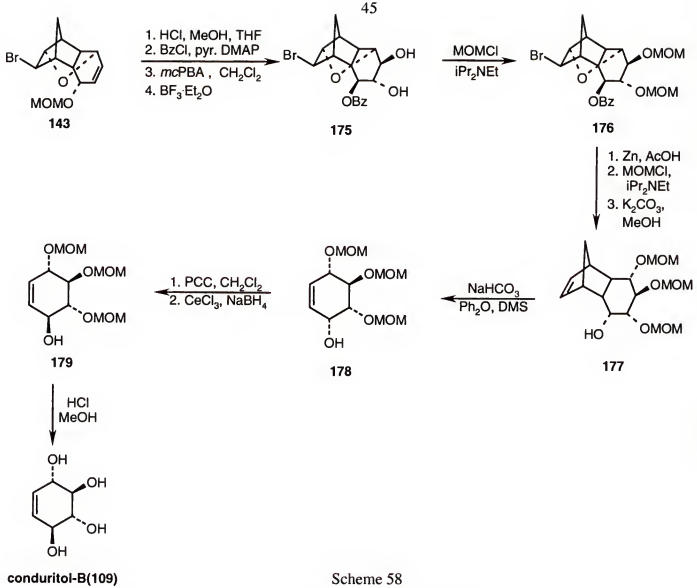


Scheme 57. Ley's synthesis of (+)-conduritol-B

of **173** provided alkene **174** in 97% yield. Removal of all protecting groups furnished conduritol-B (**109**) in quantitative yield.

More recently,[73] beginning with the same building block as for conduritol-A, the Ogasawara group was also able to prepare conduritol-B (Scheme 58).

Deprotection of ether **143**, followed by benzylation, epoxidation of the double bond and ring-opening of the epoxide under acidic conditions led to *trans*-diol **175**. The

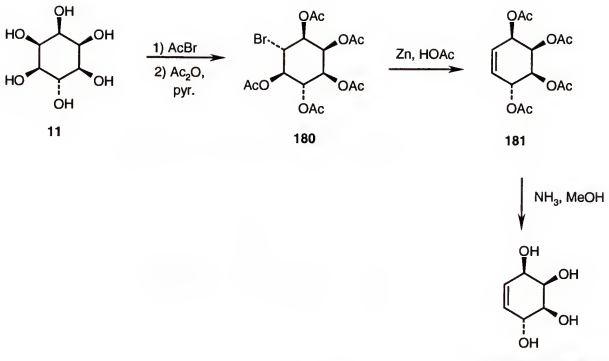


Scheme 58

hydroxyl groups were protected as MOM-ethers to give bromide **176** in 97% yield. Cleavage of the ether bridge and protection of the resulting alcohol as a MOM-ether followed by benzoate hydrolysis under basic conditions gave alkene **177**. Thermolysis of **177** gave cyclitol **178** in 96% yield which after oxidation and reduction, afforded alcohol **179**. Removal of the protecting groups gave conduritol-B in 87% yield over the last three steps.

Conduritol-C

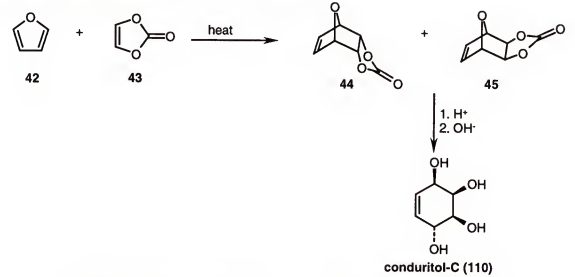
In 1955, the first synthesis of conduritol-C was completed by McCasland and Reeves (Scheme 59).[88]



Scheme 59

Heating *epi*-inositol (**11**) with acetyl bromide-acetic anhydride gave bromo-quercitol pentaacteate **180** in 35-40% yield. This intermediate was reduced with a zinc acetic acid mixture to give tetraacetate **181**, which upon ammonolysis gave conduritol-C.

Based on Kowarski's previous work, Yurev and Zefirov reported a convergent approach towards conduritol-C in 1961 (Scheme 60).[89]

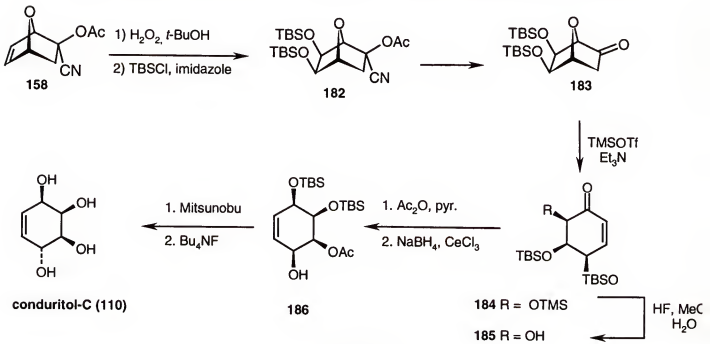


Scheme 60. The synthesis of conduritol-C by Yurev and Zefirov

Cycloaddition of furan **42** and ethylenecarbonate **43** furnished a mixture of Diels-Alder adducts **44** and **45**. Hydrolysis of both carbonates under acidic conditions gave conduritol-C (**110**).

In 1989, the Vogel research group reported their approach towards conduritol-C using the same starting material employed in their conduritol-B synthesis (Scheme 61).[90]

Dihydroxylation of nitrile **158**, followed by protection of the resulting diol gave silyl-ether **182**. Saponification produced ketone **183** in 80% yield, and ring-opening with TMSOTf furnished enone **184**. Removal of the TMS group gave alcohol **185** in 71% yield. The latter was converted to the acetate and subjected to Luche-reduction conditions

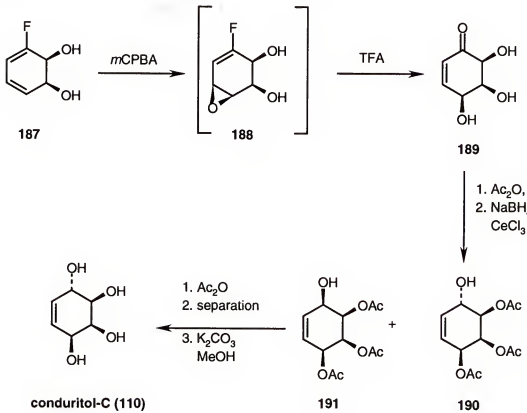


Scheme 61

to provide *cis*-alcohol **186**. Mitsunobu inversion of acetate **186**, followed by deprotection gave conduritol-C in 71% yield.

The first synthesis of (+)-conduritol-C was reported in 1991 by Carless and Oak (Scheme 62).[91]

Chiral fluorodiol **187**[92] was oxidized with *m*CPBA in the presence of trifluoroacetic acid to furnish enone **189** *via* epoxide **188** in 25% overall yield. Acetylation of **189** followed by Luche-reduction produced a 2:1 mixture of tri-acetate **190** and tri-acetate **191**, respectively. Enols **190** and **191** were separated by chroma-



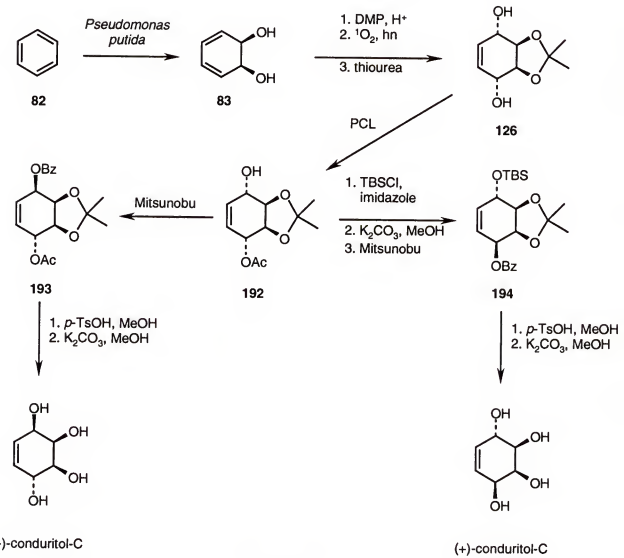
Scheme 62 Carless and Oak's synthesis of (+)-conduritol-C

tography. After acylation and deprotection of **190**, (+)-conduritol-C was obtained in 88% yield.

Johnson and co-workers synthesized both enantiomers of conduritol-C via a chemoenzymatic approach in 1991 (Scheme 63).[93]

Meso-diol **83**, obtained from the oxidation of benzene (**82**) with *Pseudomonas putida*, was protected as its acetonide, and upon singlet oxygen addition and subsequent

reduction, provided diol **126** in an overall 58% yield. Desymmetrization was achieved by acetylation of **126** with lipase from *Pseudomonas cepacia*. For the synthesis of (-)-conduritol-C, **192** was subjected to Mitsunobu conditions yielding **193** which after removal of the protecting groups furnished (-)-conduritol-C in 84% overall yield. The

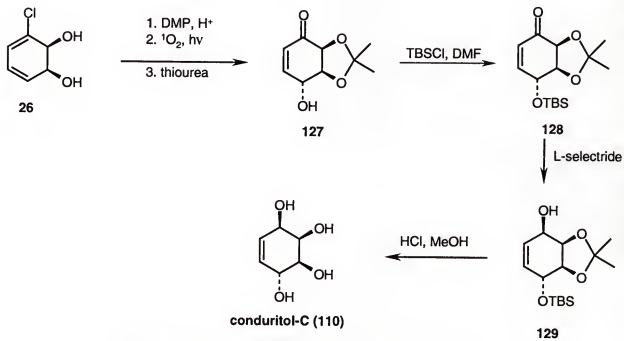


Scheme 63

(+)-isomer was obtained by protection of the free OH-group in **192** as its silyl ether, followed by acetate removal and alcohol inversion to give alkene **194**. Protecting group removal afforded (+)-conduritol-C.

The Hudlicky group prepared (-)-conduritol-C in 1991 (Scheme 64).[65]

Chiral diol **26**, obtained from biooxidation of chlorobenzene, was protected as its acetonide, subjected to photooxidation conditions and reduced to give enone **127** in 88% overall yield. After protection of the alcohol as silyl ether furnished **128**, reduction with



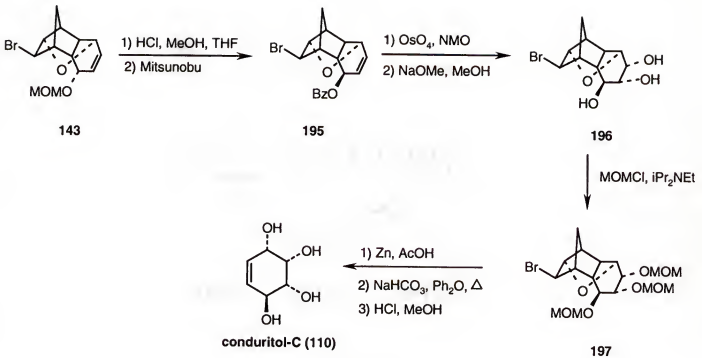
Scheme 64 . Hudlicky's synthesis of (-)-conduritol-C

L-selectride provided enol **129** in 52% yield. Deprotection under acidic conditions gave (-)-conduritol-C.

There were several other syntheses of conduritol-C reported in the nineties.[94]

In 1999 two published reports of conduritol-C were released. The first coming from the Ogasawara group who obtained conduritol-C using the same strategy described earlier (Scheme 65).[73]

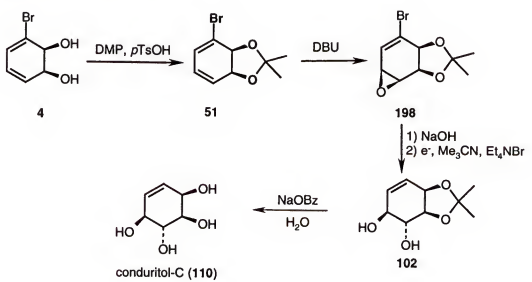
Ether 143 was deprotected under acidic conditions and converted to benzoate 195 under Mitsunobu conditions. Dihydroxylation, followed by debenzylation afforded the



Scheme 65

triol **196** which was protected as its MOM ether **197**. Reductive cleavage of the ether bridge in the presence of Zn, followed by thermolysis and removal of the protecting groups gave conduritol-C **110**.

The Hudlicky group reported an approach towards a "reagent-free" synthesis of conduritol-C (Scheme 66).[95]



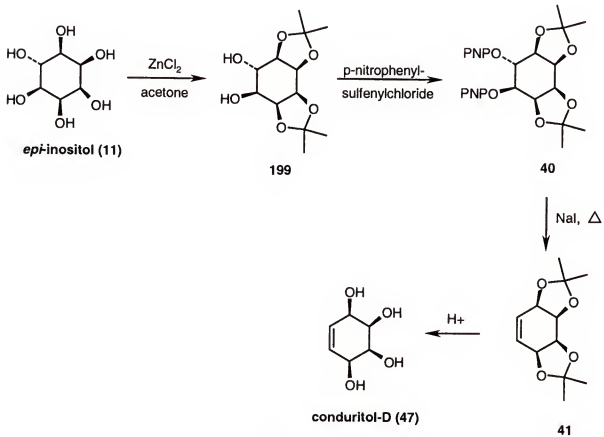
Scheme 66

Diene diol **4** was protected as its acetonide **51** and epoxidized with DBH to give bromide **198**. Opening of the epoxide under basic conditions followed by eletrochemical debromination gave diol **102**. Acetal hydrolysis gave conduritol-C in 24% overall yield.

Conduritol-D

Epi-inositol was used as starting material in Angyal and Gilham's approach to conduritol-D(Scheme 67).[96]

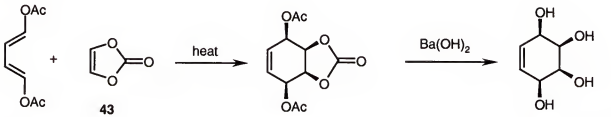
The di-*O*-isopropylidiene diol **199**, obtained from the protection of *epi*-inositol, was further protected as its *p*-nitrobenzenesulphonyloxy esters **40**. Treatment of



Scheme 67

compound **40** with NaI at elevated temperatures gave alkene **41** which was converted to conduritol-D with removal of the acetonides.

In 1957, Criegee and Becher published the synthesis of conduritol-D via a Diels-Alder approach (Scheme 68).[97]

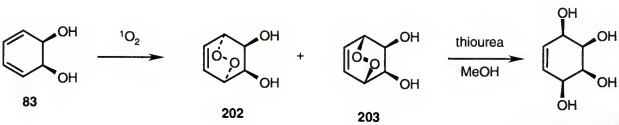


200 **43** **201** conduritol-D (47)

Scheme. 68 The synthesis of conduritol-D by Criegee and Becher

The [4+2] cycloaddition of *E,E*-diacetoxybutadiene (**200**) with ethylenecarbonate (**43**) at elevated temperatures gave diacetate **201**. Saponification of **201** afforded conduritol-D.

In the late eighties, Carless and Oak reported their chemoenzymatic approach towards conduritol-D (Scheme 69).[98]



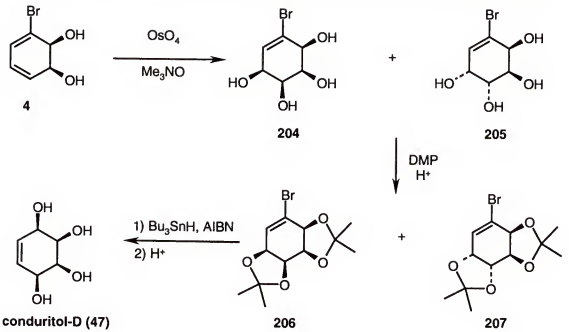
83 **202** **203** **conduritol-D (47)**

Scheme 69. The synthesis of conduritol-D by Carless and Oak

Cyclohexadiene-diol **83**, obtained by microbial oxidation of benzene, was exposed to singlet-oxygen to give a mixture of peroxides **202** and **203**, respectively. After separation, **203** was converted to conduritol-D by reduction with thiourea in methanol.

Donohoe *et al.* published their synthesis of conduritol-D in 1997 (Scheme 70).[99]

Diol **4** was oxidized, using a directed hydroxylation methodology,[100] to furnish diol **204** as the main product (82%), along with a trace amount of **205** (18%) in a total yield of 79%. Diol protection led to a separable mixture of acetonides (**206** and **207**),

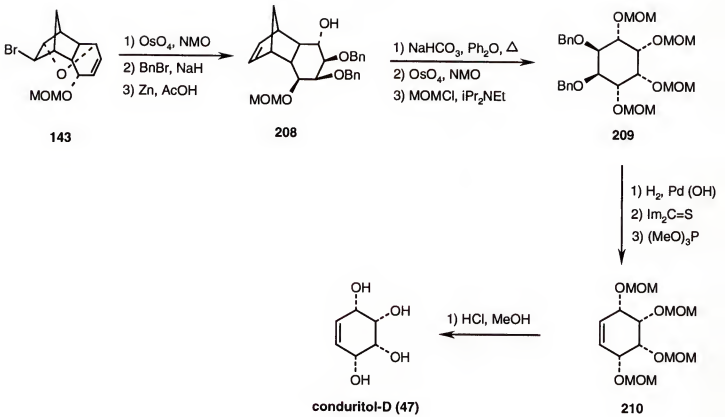


Scheme 70

which upon debromination and hydrolysis gave conduritol-D (**47**).

Ogasawara's synthesis of conduritol-D via the previously mentioned methodology began with alkene **143** (Scheme 71).[73]

Dihydroxylation of **143** followed by benzylation and reductive cleavage of the ether bridge gave alcohol **208**. Thermolysis, dihydroxylation followed by protection of the resulting diol gave cyclitol **209**. Alkene **210** was obtained by removal of the benzyl ethers, converting the resulting diol to thiocarbonate and deoxygenation. Removal of the

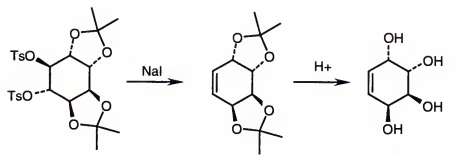


Scheme 71

protecting groups gave conduritol-D.

Conduritol-E

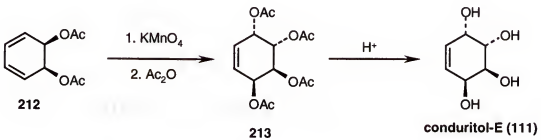
In 1955, applying a similar strategy to that used in the synthesis of conduritol-D, Angyal and Gilham reported the first stereospecific synthesis of conduritol-E (Scheme 72).[96]



Scheme 72

Ditosylate **211** was transformed to alkene **53** in the presence of NaI. Acid hydrolysis afforded conduritol-E (**111**).

Nakajima and co-workers synthesized conduritol-E in 1959 starting with diacetate **212** (Scheme 73).[101]



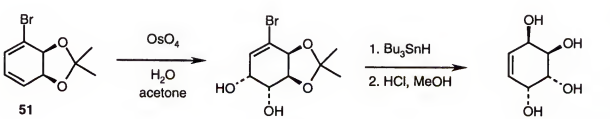
212 **213** **conduritol-E (111)**

Scheme 73. Nakajima's second synthesis of conduritol-E

Hydroxylation of diene **212** followed by acetylation of the two newly introduced OH-groups furnished tetraacetate **213**. Hydrolysis provided conduritol-E (**111**).

It was not until thirty years later that the construction of this molecule was revisited. The nineties saw more than half a dozen syntheses of conduritol-E, although many were based on previous reported methodologies.[102]

The Hudlicky research group reported their approach to conduritol-E in 1991 (Scheme 74).[103, 104]

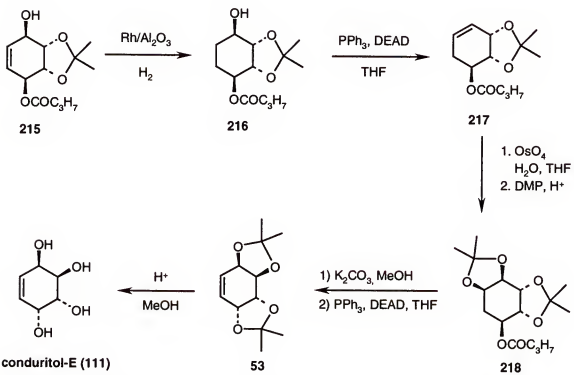


51 **214** **conduritol-E (111)**

Scheme 74

Dihydroxylation of acetonide **51** afforded diol **214** in 84% yield. Bromide reduction under radical conditions, followed by deprotection under acidic conditions furnished (-)-conduritol-E.

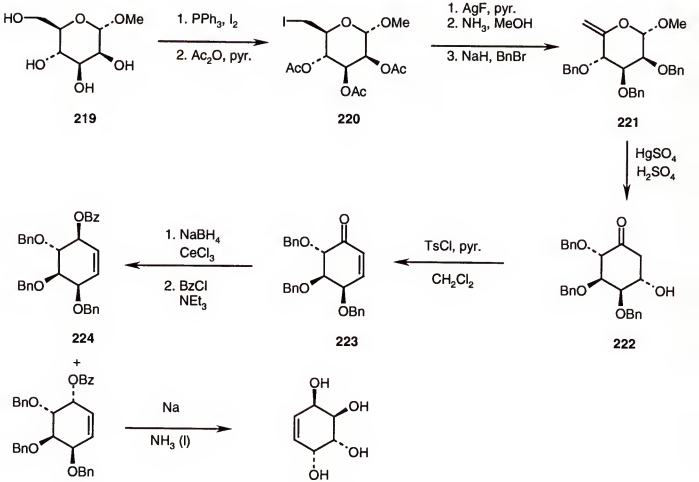
That same year, Vanderwalle and co-workers prepared (-)-conduritol-E from chiral alcohol **215** (Scheme 75).[105]



Scheme 75. The synthesis of (-)-conduritol-E by the Vanderwalle group

Hydrogenation of alkene **215** followed by elimination of the alcohol (**216**) furnished alkene **217** in 89% yield. *cis*-Hydroxylation and protection of the resulting diol as its acetonide gave **218**. After removal of the propyl ester under basic conditions, the alcohol was treated with triphenylphosphine and DEAD to accomplish dehydrogenation to give cyclohexene derivative **53**. Subsequent deprotection furnished (-)-conduritol-E in 85% yield.

In 1993, the Chapleur group prepared (-)-conduritol-E from a D-mannose derivative (Scheme 76).[106]

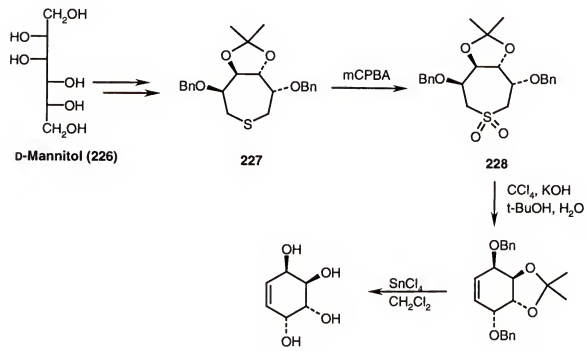


Scheme 76

Iodination of the primary alcohol of methyl-α-D-*manno* pyranoside (**219**) followed by acetylation gave iodide **220** in 91% yield. Elimination of HI was acheived with silver fluoride, followed by removal of the acetates and protection of the alcohols as benzyl ethers to give **221**. Ferrier-rearrangement of **221** furnished the cyclohexanone derivative **222**, which when tosylated, resulting in elimination giving unsaturated ketone **223**. Luche-reduction followed by benzoylation gave alkenes in 20% (**224**) and 71%

(**225**) yield, respectively. After separation by MPLC, deprotection of **225** with sodium in liquid ammonia yielded (-)-conduritol-E in 72% yield.

Improving on work done earlier in their group,[107] Cere and co-workers reported the synthesis of conduritol-E in 2000 (Scheme 77).[108]

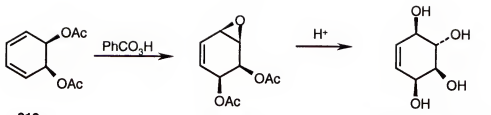


Scheme 77

Acetonide **227**, obtained from D-mannitol (**226**) was converted to sulphone **228** in the presence of *m*CPBA. Alkene **229** was acquired via the Ramberg-Backlund reaction, which upon deprotection yielded conduritol-E.

Conduritol-F

In 1962, Plouvier reported the first isolation of conduritol-F from *Chrysanthenum leucanthemum.*[109] Some three years prior, Nakajima *et al.* accomplished the first



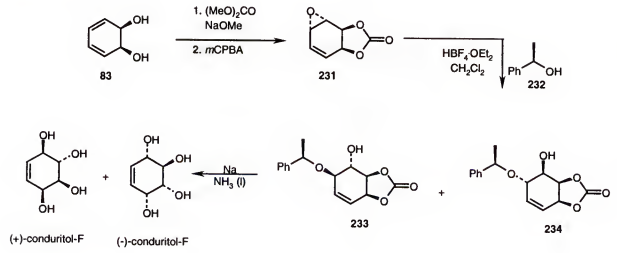
Scheme 78

synthesis of conduritol-F unaware at the time that it could be obtained from natural resources (Scheme 78).[101]

Expanding on the methodology used to construct conduritol A, B, and E, diene-diacetate **212** was oxidized to its epoxide **230** with peracid. Acidic hydrolysis furnished conduritol F (**112**).

There was only one synthesis of condurtol-E between 1962 and a resurgence of interest in this compound in the 1990's.[110] As with conduritol-E, this decade produced several synthetic approaches to conduritol-F, many by groups expanding on previously developed methodologies.[111]

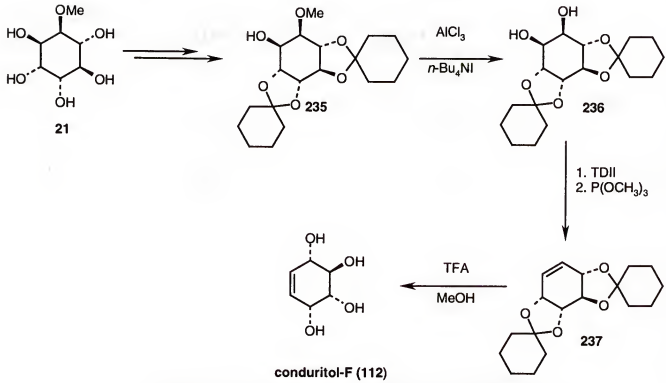
In 1990, both enantiomers of conduritol-F were prepared by the Ley research group (Scheme 79).[112]



Scheme 79

Diene-diol **83** was converted to its carbonate, followed by epoxidation yielding vinyl oxirane **231** in 47% overall yield. Regioselective ring opening of **231** with (*R*)-*sec*-phenethyl alcohol (**232**) gave a 1:1 mixture of isomeric alcohols **233** and **234** (67%). Deprotection afforded both (+)- and (-)-conduritol-F in 80% and 85% yield, respectively.

In 1991, Ozaki and co-workers reported the synthesis of the (-)-enantiomer of conduritol-F (Scheme 80).[85]

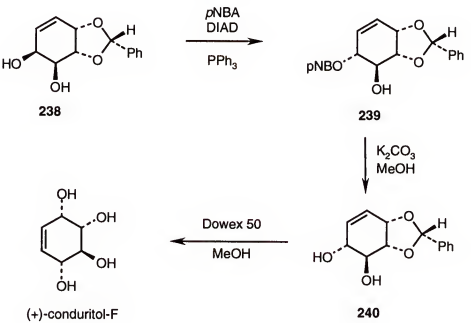


Scheme 80. The synthesis of (-)-conduritol-F by Akiyama *et al.*

Protection of L-quebrachitol (**21**) gave alcohol **235** which was demethylated using aluminum chloride and tertbutylammonium iodide to give diol **236** in 78% yield. Conversion of **236** to thiocarbonate, followed by treatment with trimethylphosphite furnished cyclohexene derivative **237** (90% for two steps). Deprotection of alkene **237** under acidic conditions provided (-)-conduritol-F in 90% yield.

In 1995, Yoshimitsu and Ogasawara prepared (+)-conduritol-F, starting from a conduritol-E derivative (Scheme 81).[113]

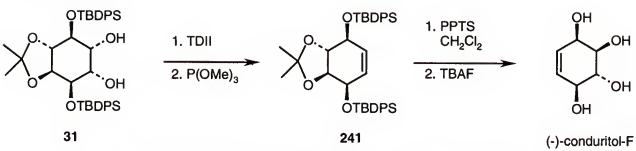
Treatment of 1,2-*O*-Benzylidene conduritol-E (**238**) under Mitsunobu conditions with *p*-nitrobenzoic acid (*p*NBA) and diisopropyl azodicarboxylate furnished alcohol **239**



Scheme 81 The synthesis of (+)-conduritol-F by Yoshimitsu and Ogasawara

in 79% yield (87% ee). Removal of the *p*-nitrobenzoate provided **240** (81%) which, upon treatment with ion-exchange resin gave (+)-conduritol-F (80%).

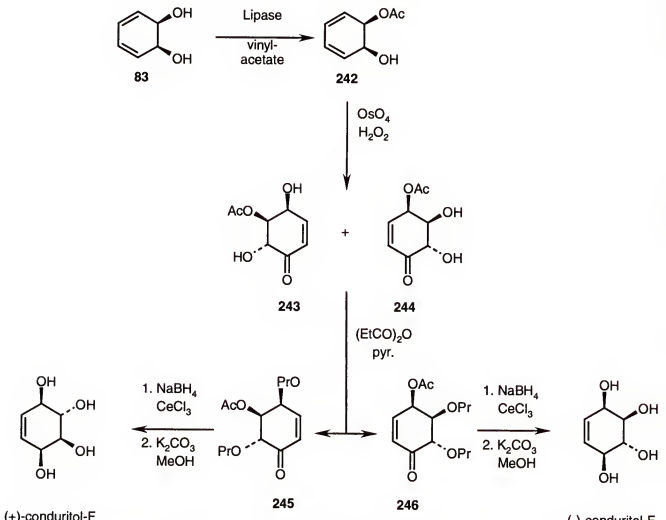
That same year, Chiara and Valle published their synthesis of (-)-conduritol-F (Scheme 82).[114]



Scheme 82. The synthesis of (-)-conduritol-F by Chiara and Valle

Diol **31**, an intermediate previously synthesized in their approach to L-*chiro*-inositol, was subjected to Barton deoxygenation conditions to give cyclohexene derivative **241** in 79% yield. Deprotection of **241** furnished (-)-conduritol-F.

In 1996, an enantioselective synthesis of both isomers of conduritol-F was published by the Nicolosi group (Scheme 83).[115]

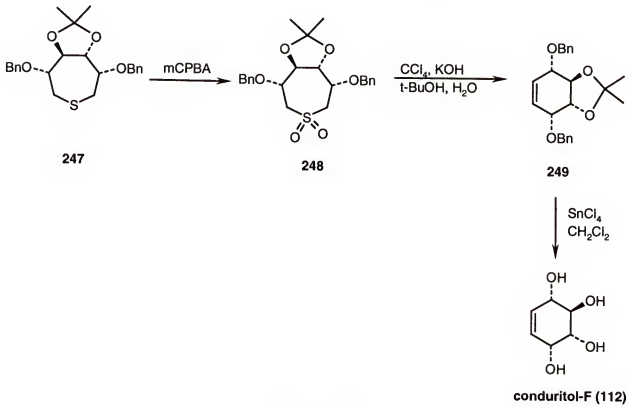


Scheme 83. The synthesis of (+)- and (-)-conduritol-F by Nicolosi *et al.*

Enzymatic acetylation of diene-diol **83** gave chiral alcohol **242** in 89% yield (>98% ee). Hydroxylation under Milas-conditions[116] produced a 3:2 mixture of diastereomers **243** and **244**. Acylation with propionic anhydride allowed for separation

gave a mixture of enone **246** (48%) and **245** (32%), respectively. Both isomers were subjected to Luche-reduction, followed by deprotection to afford (+)- and (-)-conduritol-F in 90% and 88% yield, respectively.

Incorporating their approach used in the synthesis of conduritol-E, Cere and co-workers prepared (-)-conduritol-F in a similar fashion (Scheme 84).[108]



Scheme 84

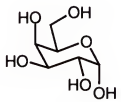
Thioether **247** was oxidized to the sulfone **248** with *m*CPBA and subjected to Ramberg-Backlund reaction conditions. Dibenzyl **249** was fully deprotected to give (-)-conduritol-F (**112**).

Inositol Oligomers

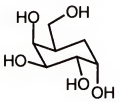
Introduction

Pseudo-sugars have received the attention of the synthetic community because of their therapeutic potential. The term "pseudo-sugar" refers to a class of compounds in

which the ring oxygen of a sugar is replaced by a methylene group. G.E. McCasland first proposed the term in 1966.[117] In his paper he suggested that due to their structural resemblance to natural sugars, they may possess some biological activity; he was correct.



(250) α-D-galactopyranose



(251) pseudo-α-D-galactopyranose

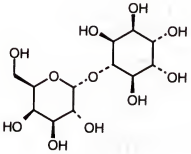
Figure 6 Structure of natural and pseudo sugars

The first naturally occurring pseudo-sugar; pseudo-α–D-galactopyranose **251** was discovered to possess antibiotic properties (Figure 6).[118] Other derivatives have also shown biological activity ranging from inhibition of a glucose-stimulated insulin release to possible activity in cell adhesion and communication pathways.[119]

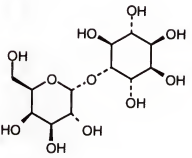
In 1986, the detection of two insulin mimetic phosphorylated inositol glycosides in rat hepatocytes caught the attention of some members of the synthetic community.[120] Also know as glycophosphatidyl inositols (GPI) or phosphooligosaccharides (POS), these molecules have been reported to be involved in the anchoring of various cell-surface proteins to membranes as well as transmembrane signaling of insulin.[121]

Upon activation, the anchored protein is cleaved to release the biologically active protein and the inositol glycan fragment. It has been suggested that following the interaction of insulin with the cell surface receptor, one or more phosphorylated inosityl-glycans are released as putative insulin mediators, which can mimic some biochemical

activities of insulin *in vitro*.[122] Some examples of nature's inositol glycosides are shown in Figure 7.



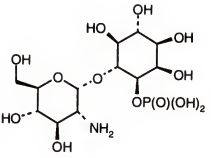
252



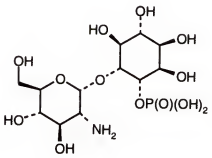
253

Figure 7. Structure of natural glycosides

Putative mimics **254** and **255** have been synthesized by several groups[123] and have shown modest insulin mediating properties (Figure 8).



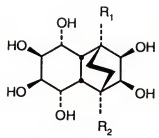
254



255

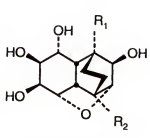
Figure 8 Structure of insulin mimics

In 1994 Billington and co-workers synthesized all six isomeric conduritols and a range of polycyclic analogues of conduritol-A and examined their ability to modify insulin release *in vitro* (Figure 9).[124]



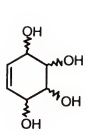
(256) $R_1 = H, R_2 = H$

(257) $R_1 = CH_3, R_2 = CH(CH_3)_2$



(258) $R_1 = H, R_2 = H$

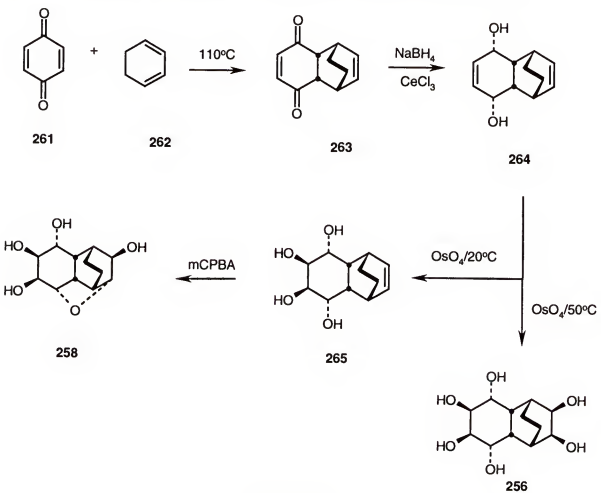
(259) $R_1 = CH_3, R_2 = CH(CH_3)_2$



260

Figure 9 Billington's analogues

Cycloaddition of benzoquinone (**261**) with 1,3-cyclohexadiene (**262**) at 110°C in toluene gave adduct **263** (Scheme 85). Stereoselective reduction with cerium (III)

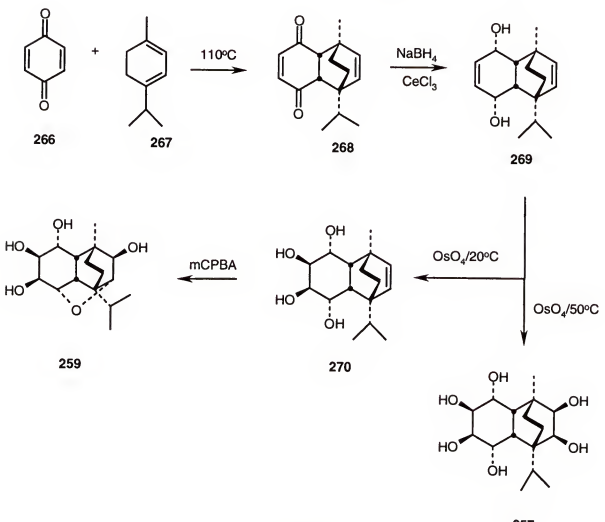


261 **262** **263** **264** **265** **256** **258**

Scheme 85

chloride/$NaBH_4$ afforded *cis*-diol **264**. Osmylation of diene **264** at higher temperatures yielded hexol **256**, while treatment of **264** with OsO_4 at 20°C gave selectively tetrol **265**. Target molecule **258** was obtained when alkene **265** was treated with *m*CPBA, resulting in an intramolecular opening of the epoxide by the proximal OH group.

Tricyclic polyols **257** and **259** were obtained in a similar fashion (Scheme 86).

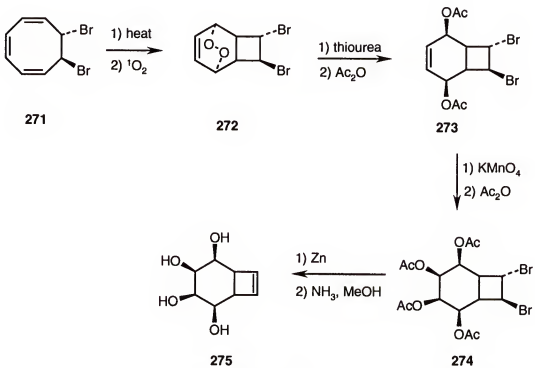


Scheme 86

Cycloaddition of benzoquinone (**266**) with γ-terpinene (**267**) afforded diels-alder adduct **268**. Stereoselective reduction with cerium (III) chloride/$NaBH_4$ furnished *cis*-diol **269**. Osmylation of diene **269** at higher temperatures yielded hexol **257**, while

treatment of **269** with OsO_4 at 20°C gave tetrol **270** selectively. Ether **259** was obtained when alkene **270** was treated with *m*CPBA, resulting in an intramolecular opening of the resulting epoxide by the proximal alcohol. It was found that conduritols A, B, and their derivatives were able to modulate the release of insulin from isolated pancreatic islets in the presence of varying concentrations of glucose.

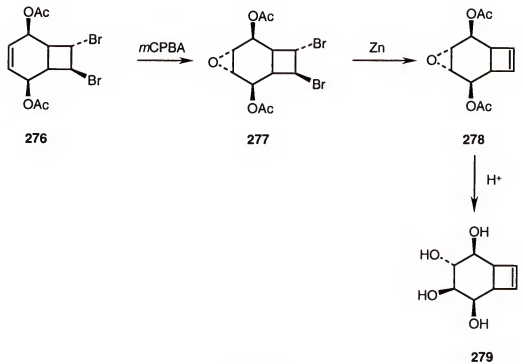
Three years later, the Balci group also published the synthesis of all conduritol isomers along with other conduritol D and F analogues.[125]



Scheme 87

Heating bicyclooctatriene **271** followed by photooxygenation gave access to endoperoxide **272** (Scheme 87). Thiourea reduction followed by protection with acetic anhydride yielded diacetate **273**. Oxidation of the double bond followed by protection of the resulting diol as its acetate derivative afforded tetraacetate **274**. Zn-mediated elimination, followed by ammonolysis gave the unsaturated cyclitol **275.**

Conduritol-F analogue **279** was obtained in a similar fashion (Scheme 88).



Scheme 88

Diacetate **276** was treated with *m*CPBA to give epoxide **277** as an only isomer. Zn-mediated elimination (**278**) followed by acidic hydrolysis gave tetrol **279** in high yield.

In the late nineties, Mehta and co-workers designed several polycyclitols as potential glycomimics. A wide range of carbocyclic analogues of carbohydrates and aza-

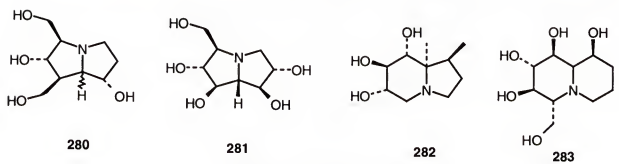


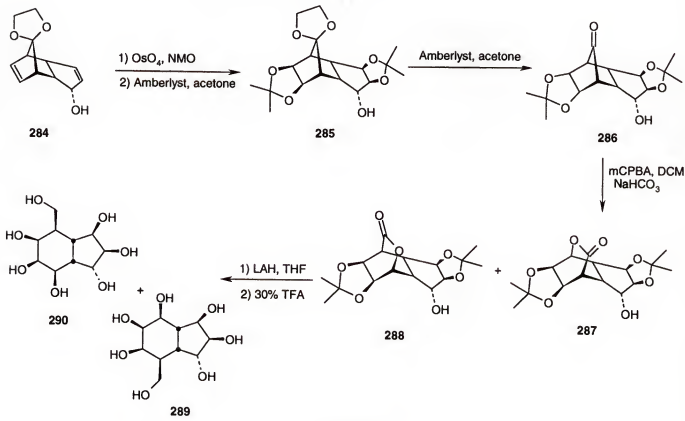
Figure 10 Structure of Aza-sugars

carbasugars as well as indolizidine alkaloids were synthesized and tested for glycosidase inhibition properties. Recent studies of polyhydroxylated pyrrolizidine, indolizidine and

quinolizidine alkaloids have shown that these natural products contain a wide range of biological activities as well (Figure 10).[126] These alkaloids exhibit activities such as anti-viral, anti-cancer as well as specific inhibitory activity against glycosidases.

In 1999, the Mehta research group synthesized a series of carbocyclic equivalents of these biologically active compounds and evaluated them as potential glycomimics.[127]

The first set of indolizidine related compounds were synthesized starting with a dicyclo-pentadiene analog (Scheme 89).

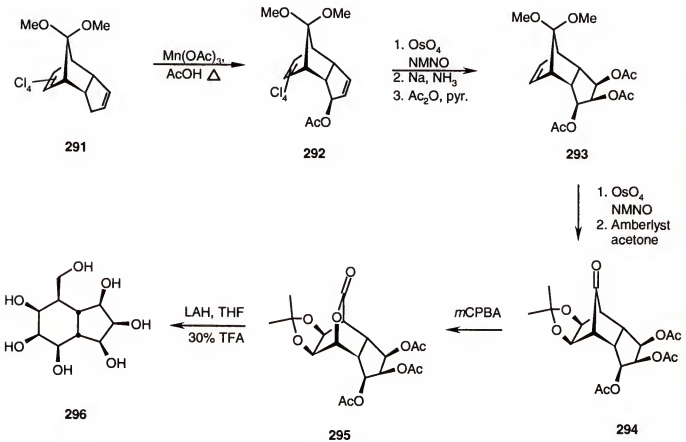


Scheme 89

Enatiomerically pure alcohol **284** was obtained via kinetic enzymatic acylation.[128] Catalytic *cis*-dihydroxylation of both double bonds followed by protection furnished the bis-acetonide **285**. Transacetalisation of **285** led to keto-acetonide **286**. Regioisomeric lactones **287** and **288** were obtained via a Baeyer-Villiger oxidation with *m*CPBA.

Reduction with LAH, followed by acetal hydrolysis gave polycyclitols **289** and **290** respectively.

An all *cis*-derivative of cyclitol **290** was synthesized beginning with diels-alder adduct **291**, obtained from heating 5,5-dimethoxy-tetrachlorocyclopentadiene and cyclopentadiene in toluene (Scheme 90).

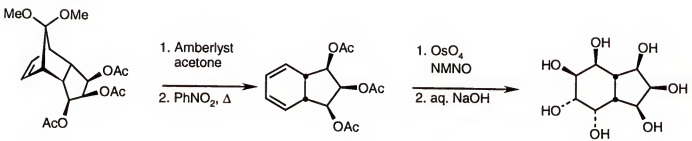


Scheme 90

Exo-acetate **292** was obtained via oxidation of diene **291** with manganese (III) acetate. Selective *cis*-dihydroxylation, reductive dehalogenation, and acetylation provided triacetate **293**. Keto-acetonide **294** was obtained by dihydroxylation with catalytic OsO_4, acetal deprotection and diol protection. Bridge cleavage was

accomplished through a Baeyer-Villiger oxidation which furnished a single lactone **295** in good yield. LAH reduction and acetonide deprotection gave the desired bicyclitol **296**.

In 2001, Mehta and Ramesh published the synthesis of four new indolizidine polycyclitols[129] based on the work done in 1999 (Scheme 91).

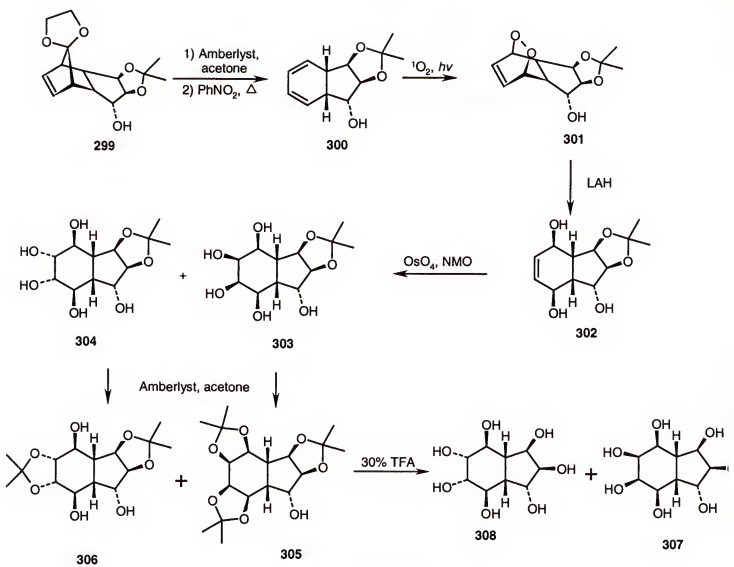


293 **297** **298**

Scheme 91

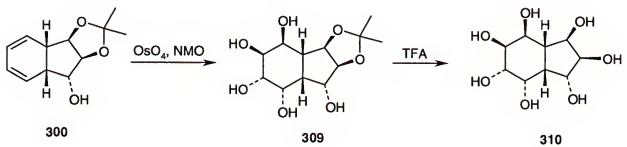
Triacetate **293**, previously obtained, was converted to diene **297** in two steps via acetal deprotection and thermally-induced decarbonylation. Double dihydroxylation followed by mild base hydrolysis of the resulting triacetate afforded heptahydroxy compound **298**.

Ketal deprotection of acetonide **299** followed by thermal decarbonylation of the resulting ketone gave diene **300** as depicted on the next page (Scheme 92). Singlet oxygen addition to the diene resulted in [4+2]-cycloaddition and afforded endoperoxide **301**. Lithium aluminum hydride reduction provided triol **302**, which upon osmylation afforded a 3:1 mixture of pental **303** and **304**. Separation and conversion to the tri and bis-acetonide respectively led to cyclitols **305** and **306**. Hydrolysis of the acetonide moieties furnished diastereo-isomeric hepta-hydroxy hydrindanes **307** and **308**.



Scheme 92

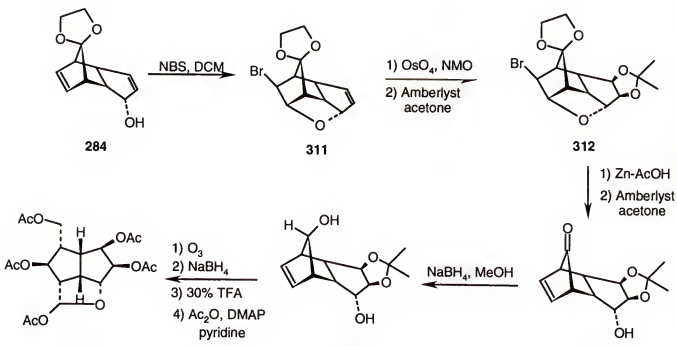
A fourth and final indolizidine related compound was obtained from diene **300** (Scheme 93).



Scheme 93

Dihydroxylation of both double bonds gave access of pentol **309**. Removal on the acetonide with TFA afforded cyclitol **310**.

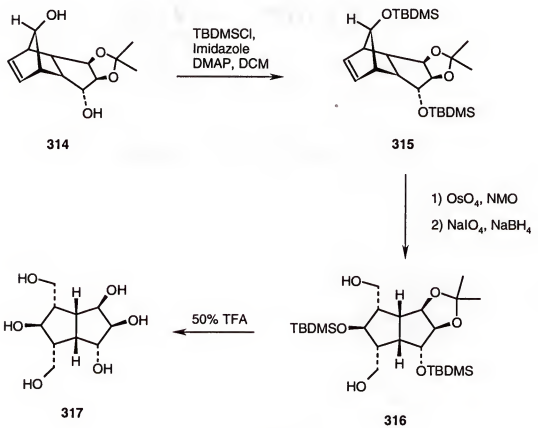
In 1999, Mehta also published the synthesis of two pyrrolizidine and one quinolizine carbocyclic related compounds. [130] The approach to diquinane based polyols began with previously synthesized enatiomerically pure endo-tricyclic allylic alcohol **284** (Scheme 94).



Scheme 94

Protection of the norbornene double bond through intramolecular etherification gave bromide **311**. Osmylation of the double bond followed by protection furnished acetonide **312**. Reductive removal of the bromide in the presence of Zn and acetal deprotection afforded alcohol **313**. Hydride reduction of the ketone furnished diol **314**, which was subjected to ozonolysis, reductive work-up, acetal deprotection and acetylation to give penta-acetate **315**.

The acetate-free derivative of **315** was obtained starting with diol **314** which was protected as its TBDMS ether to furnish acetonide **315** (Scheme 95). A three-step

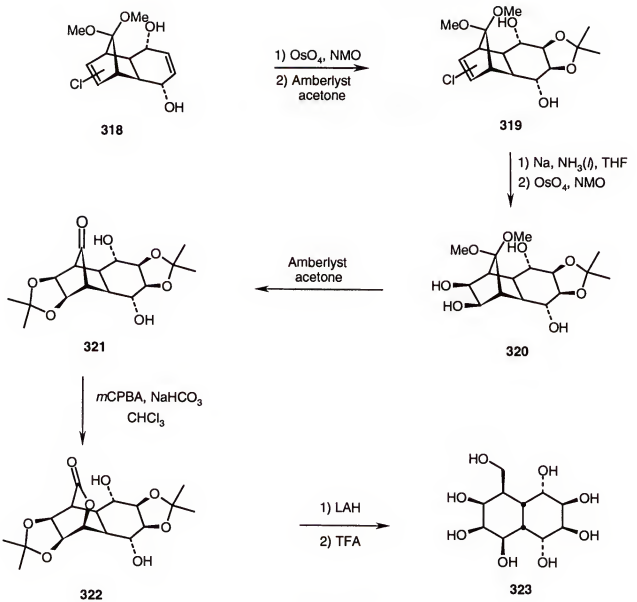


Scheme 95

sequence involving dihydroxylation, periodate cleavage and hydride reduction furnished diol **316**. Removal of the protecting groups gave hexahydroxy diquinone **317**.

In the same publication, beginning with diol **318**, obtained by literature procedures,[131] the Mehta group synthesized a decalin based polyol (Scheme 96).

Osmylation of the cyclohexene double bond followed by protection gave acetonide **319**. Reductive dehalogenation and osmylation of the remaining double bond gave tetrol **320**. A one-pot acid catalyzed acetal-deprotection and 1,2-diol protection



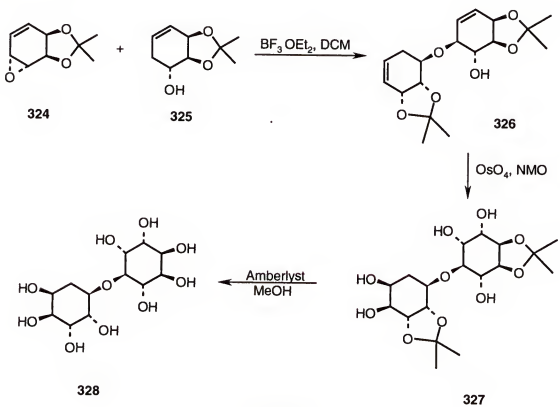
Scheme 96

gave keto- diacetonide **321**. Bayer-Villiger oxidation provided lactone **322**, which was reduced with LAH and deprotected with TFA to give octa-hydroxy decalin **323**.

Synthesis of Cyclitol Oligomers

In the middle and late nineteen nineties, the Hudlicky group synthesized a wide range of polyoxygenated sugar and conduritol analogs. In 1994,[132] Hudlicky and co-workers published the synthesis of L-*chiro-gala*-quercitol conjugate **328** and in the

process developed a methodology that has provided access to a variety of cyclitol derivatives.



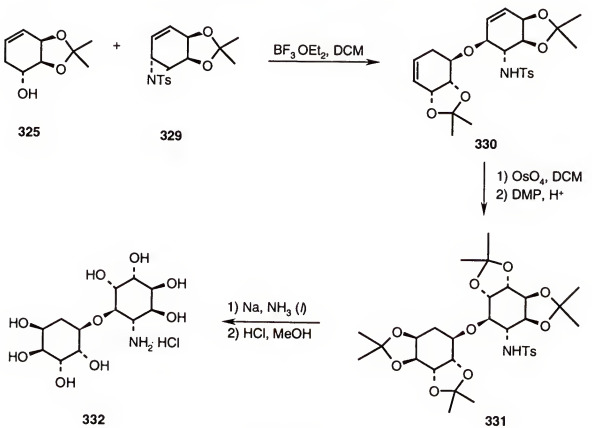
324 **325** **326** **327** **328**

Scheme 97

Opening of epoxide **324** with alcohol **325**, under acidic conditions, afforded diene **326** in 75% yield (Scheme 97). *cis*-Hydroxylation of ether **326** with OsO_4 yielded pentol **327** in 74% yield. Deprotection of the two isopropylidene groups under acidic conditions gave the L-*chiro*-inositol-*gala*-queritol adduct **328** in 98% yield.

Two years later, the Hudlicky group expanded on this work and synthesized higher oligomers of L-*chiro* inositol conjugated to other inositols or amino cyclitols and reported the interesting properties of these novel classes of compounds.[133] Some of the molecules synthesized in this publication are presented below.

Opening of vinyl aziridine **329** with alcohol **325** in the presence of BF_3OEt_2, gave diene **330** in 52 % yield (Scheme 98). Oxidation of the diene with OsO_4 followed by

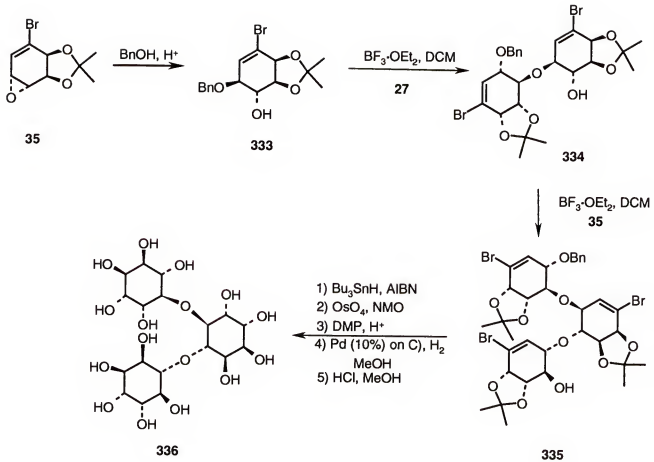


325 **329** **330** **331** **332**

Scheme 98

protection of the resulting alcohols with DMP gave the acetonide **331**. Removal of the tosyl group with sodium in liquid ammonia, followed by quantitative removal of the acetonide in methanolic HCl yielded the amine hydrochloride **332**.

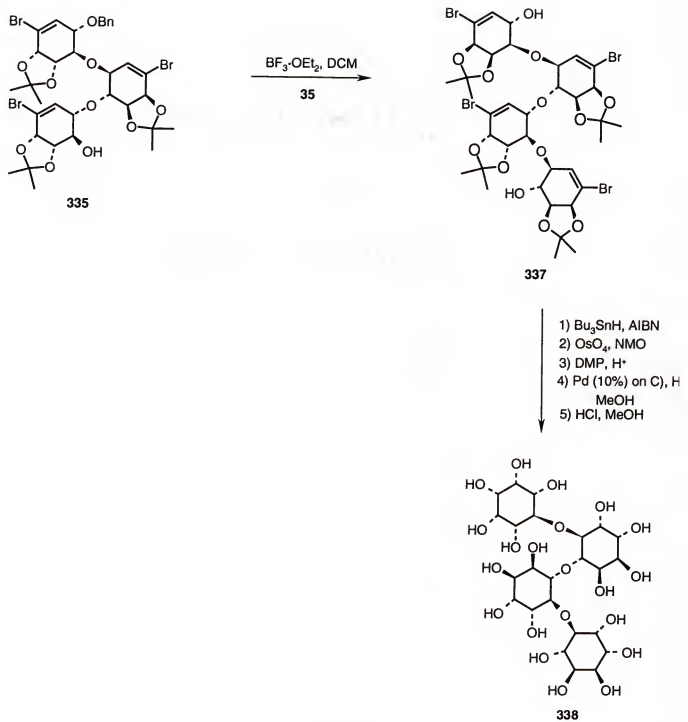
Coupling of alcohol **333** with epoxide **35** under Lewis acid conditions afforded alcohol **334** in 55% yield (Scheme 99). Alcohol **334** was then coupled with a second equivalent of epoxide **35** to furnish tricyclitol **335**. Polyoxygenated triene **336** was obtained via an ordered reaction sequence that included debromination, oxidation of the



Scheme 99

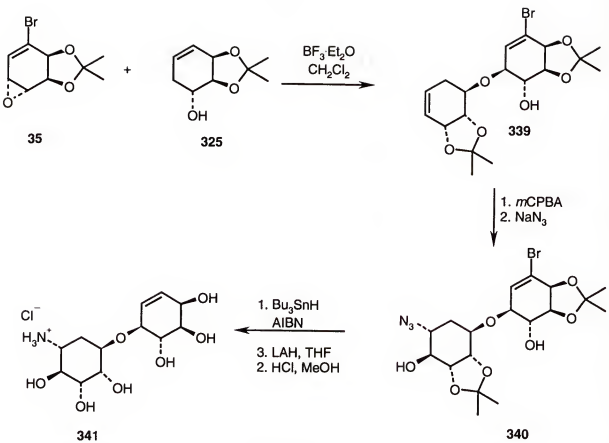
resulting diene followed by protection, and removal of all protecting groups.

Tetramer **338** was also synthesized via this route as well (Scheme 100) . Triene **335** was reacted with epoxide **35** under Lewis acid conditions to afford diol **337**. Tetracyclitol **338** was obtained via an ordered reaction sequence that included, debromination, oxidation of the resulting diene followed by protection, and removal of all protecting groups.



Scheme 100

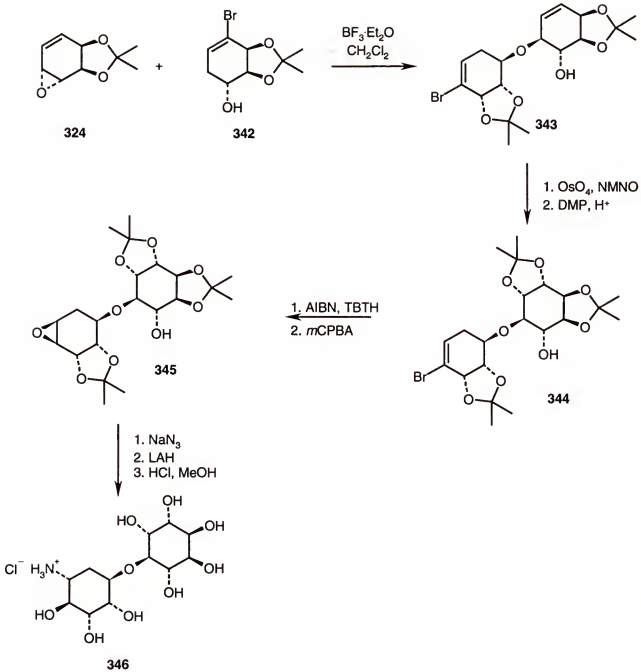
Opening of epoxide **35** under acidic conditions with alcohol **325** as the nucleophile gave bromide **339** (Scheme 101). Epoxidation of the unsubstituted alkene followed by azide opening gave azido-diol **340**. Radical debromination, azide re-



Scheme 101

duction followed by treatment with methonolic HCl gave conduramine hydrochloride **341**.

An aceto-hydroxy derivative of **341** was obtained in a similar fashion (Scheme 102). Opening of epoxide **324** with bromo-alcohol **342** gave diene **343**. *cis*-Hydroxylation followed by protection yielded alcohol **344**. Radical debromination followed by epoxidation with *m*CPBA afforded epoxide **345**. Target compound **346**

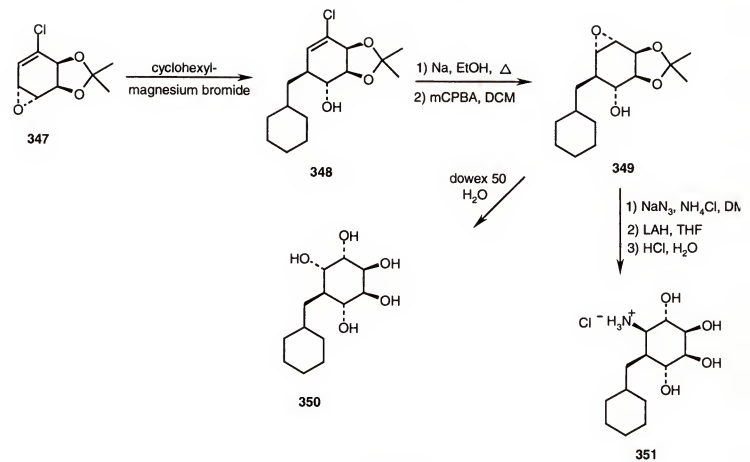


324 + **342** → **343** → **344** → **345** → **346**

Scheme 102

was obtained via azide opening of **345** followed by hydride reduction and acid hydrolysis of the protecting groups.

In the same publication, the synthesis of C-linked pseudodisaccarides were described (Scheme 103).



Scheme 103

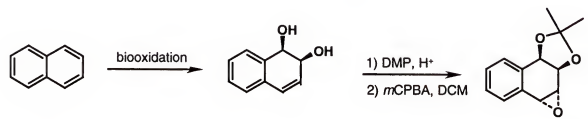
Opening of epoxide **347** with cyclohexylmagnesium bromide gave alcohol **348**. Sodium metal removal of the chloride followed by epoxidation with *m*CPBA, gave alcohol **349**. Pentol **350** was obtained by opening of epoxide **349** under acidic conditions, while azide opening of **349**, followed by reduction and acid catalyzed deprotection afforded amine hydrochloride **351**.

Several of these polyoxygenated compounds appeared to be ideal candidates for testing as enzyme inhibitors. Cyclitol **328** and amine-inositol **332** were tested for the inhibition of almond β-glucosidase and β-mannosidase against the glycosidase-catalyzed hydrolysis of respective *p*-nitrophenylpyranoside. It was found that amino cyclitol **332**

inhibited β-glucosidase by 12% at 3.5 mMol concentration, while inositol conjugate **328** displayed no level of activity against these enzymes.

In 1997, the Hudlicky group revisited this methodology and applied it to the synthesis of a range of polycyclic conduritols and conduramines as well as poly-hydroxylated tetrahydronaphthalene ethers.[134]

Biooxidation of naphthalene **352** with toluene dioxygenase expressed in *Escherichia* coli JM109 (pDTG601) afforded *cis*-diol **353** in a yield of 7.5 g/L of broth (Scheme 104). Diol **353** was protected as its isopropylidiene derivative using

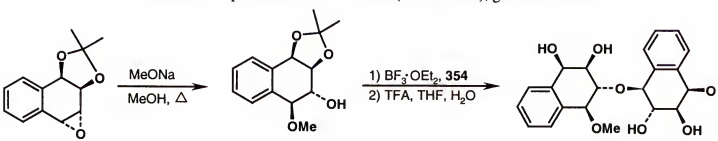


352 **353** **354**

Scheme 104

2,2-dimethoxypropane with catalytic amount of *p*-toluensulfonic acid. Epoxidation with *m*-chloroperoxybenzoic acid in methylene chloride afforded **354** in 70% yield. Opening of this key intermediate under Lewis acid conditions with a variety of nucleophiles allowed for the synthesis of four new dimeric conduritol analogs.

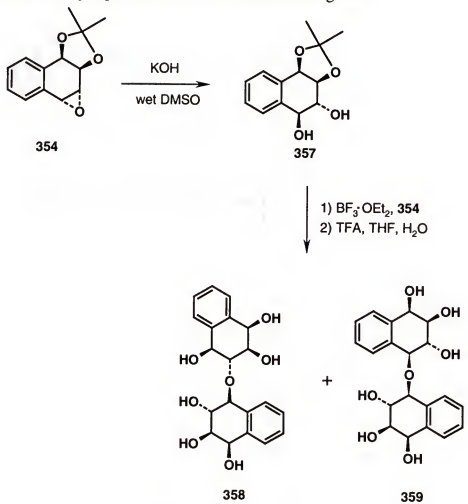
Treatment of epoxide **354** with NaOMe (Scheme 105), gave alcohol **355**.



354 **355** **356**

Scheme 105

Nucleophilic opening of a second equivalent epoxide **354** with alcohol **355,** under Lewis acid condition followed by deprotection lead to conduritol analog **356.**

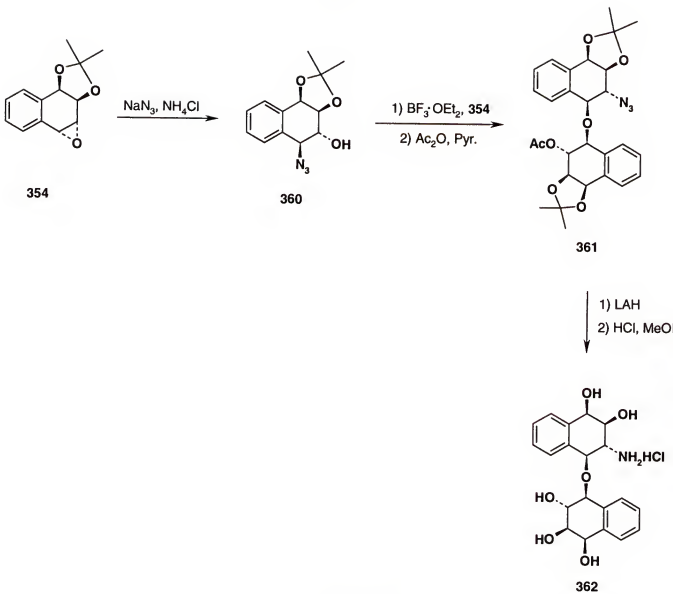


Scheme 106

Opening of epoxide **354** with KOH afforded *trans*-diol **357**. Opening of a second equivalent of epoxide **354** with **357** followed by deprotection afforded conduritol analogs **358** and **359** (Scheme 106).

The synthesis of conduramine analogs was achieved using the same chemical strategy (Scheme 107).

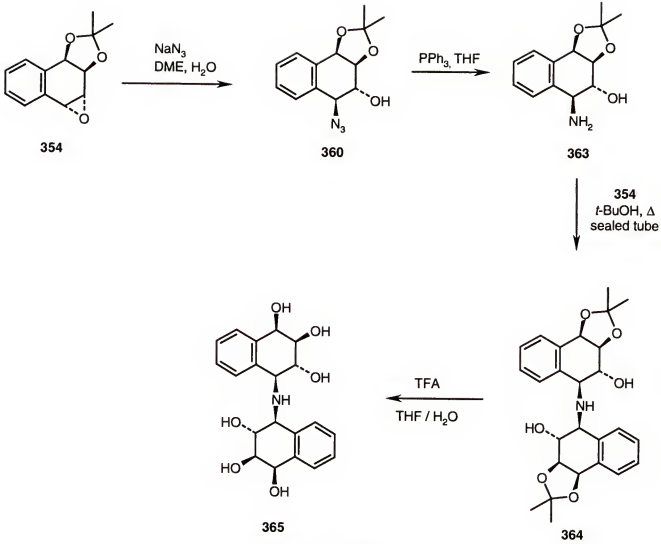
Coupling of azido alcohol **360** with epoxide **354**, gave ether **361**. Protection of the alcohol as its acetate derivative with acetic anhydride afforded bis-isoproylidene



Scheme 107

361. Reduction of the azide functionality, as well as deprotection of the acetyl group with lithium aluminum hydride followed by removal of the acetonide in acidic medium gave conduramine analog **362** as its hydrochloride salt.

Ring opening of epoxide **354** was achieved with sodium azide, which gave azido-alcochol **360** (Scheme 108). Reduction of the azide under Staudinger conditions furnished primary amine **363**. Amine **363** was reacted with epoxide **354** in t-BuOH at elevated temperature to produce N-linked dimer **364** in 50% yield. Compound **364** was



Scheme 108

deprotected under acidic conditions to yield free N-linked tetrahydronaphthalene dimer **365** (90%).

These compounds were then tested for glycosidase inhibition. Due to their low solubility in H_2O, compounds **356**, **358**, and **359** were not viable candidates for enzymatic assays. Conduramine analog **362**, whose solubility problem was overcome with the presence of an amino hydrochloride, did not show any activity against β-mannosidase, α-galactosidase or β-galactosidase.

Molecular Properties

Several of the synthesized oligomers were studied theoretically. Three dimensional molecular dynamic simulations of dimer **326**, trimer **334**, and tetramer **336**

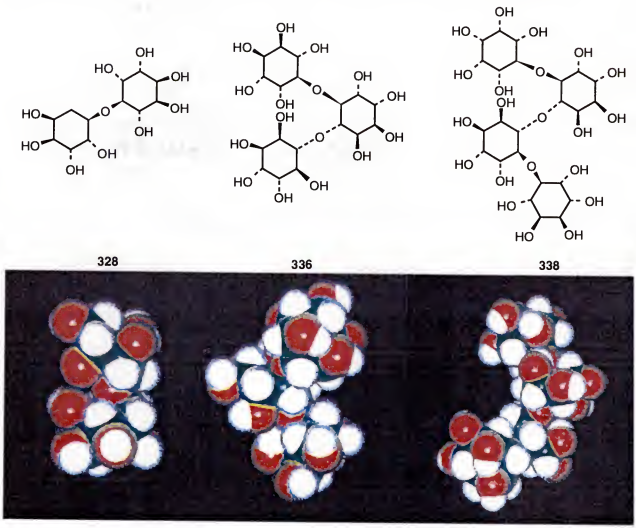
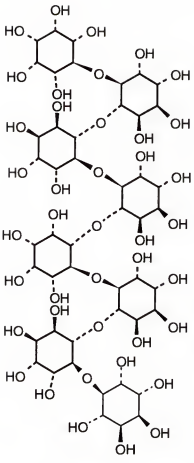


Figure 11 Inositol structures and modeling simulation

suggest an increasing tendency with length toward a reverse-turn like structure similar to that of polypeptides (Figure 11). Although the L-*chiro* inositol tetramer has a turn like



366

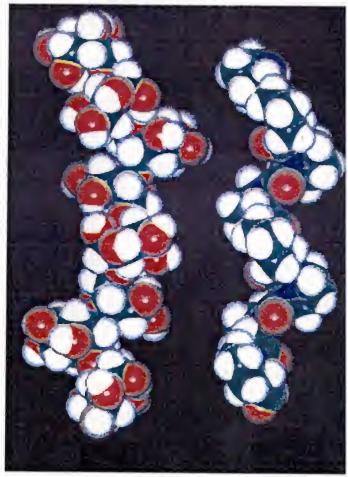
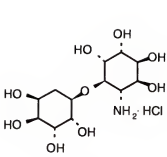


Figure 12 Inositol Octomer and simulation

appearance, the octamer displays a helical appearance, comparable to that of L-proline (Figure 12).

The metal-chelating potential of oxygen-linked amino cyclitol **332** was also tested. Doping of an aqueous solution of the amine-hydrochloride **332** with an equimolar aqueous solution of calcium chloride, followed by slow evaporation yielded crystals which were analyzed by single crystal X-ray diffraction (Figure 13). The results showed that compound **332** possessed an extended helical structure, exhibiting an ordered array of calcium ions bridging two amino-cyclitol residues. This resulting in the dimers



332

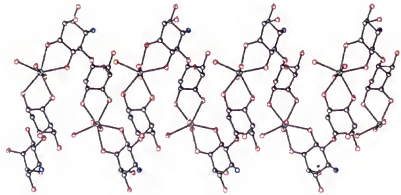


Figure 13 Crystal lattice of amino-cyclitol **332**

forming a compact and symmetrical structure which is energetically favorable as a crystal lattice.

Inositol Signaling Pathways

Introduction and Historical

In 1975, Robert Michell suggested that phosphatidylinositol-4,5-bisphosphate (PIP_2) hydrolysis was somehow associated with Ca^{2+} release.[135] Investigations notably by Hokin,[136] Michael Berridge,[137] and Michell have revealed that PIP_2 is part of an important second messenger system known as phosphoinositide (PI) cascade.

Second messengers are molecules that relay signals received at the cell surface. The phosphoinositide system is stimulated by an agonist such as a hormone or growth factor (Figure 14). The receptor is coupled to a G-protein or tryrosine kinase-linked receptor which translates the signal by activating a phospholipase C (PLC) inside the cell. The activated PLC then hydrolyzes a phosphorylated phosphatidylinositol, generated by

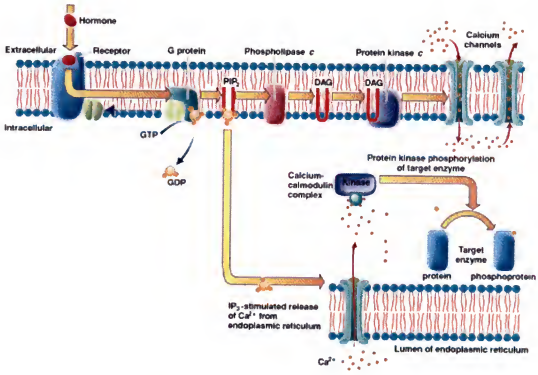
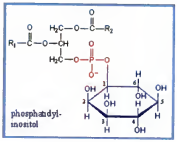
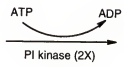


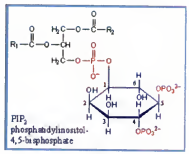
Figure 14

the sequential transfer of 2 phosphates from ATP to PI (Scheme 109). This generates two second messengers, inositol-1,4,5-trisphosphate (IP_3) **370** and diacylglycerol (DAG) **369**



367

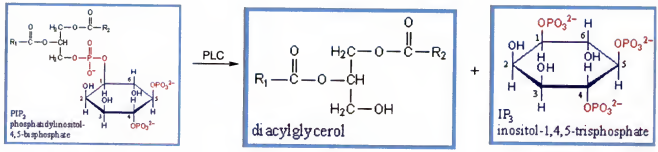




368

Scheme 109

(Scheme 110). IP_3 is a water soluble, small molecule. The IP_3 receptor, a ligand-gated calcium channel in the endoplasmic recticulum (ER), binds IP_3, and calcium ions



368 **369** **370**

Scheme 110

are released into the cytosol. Calcium binds, two to each globular end, to a protein known as calmodulin. The Ca-calmodulin complex changes conformation and then wraps around the calmodulin-binding site of target proteins to activate a number of processes (Figure 15).

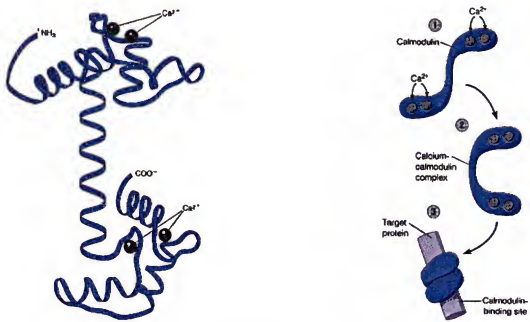


Figure 15

DAG stays in the plane of the membrane and activates protein kinase C (PKC). Protein Kinase C is an enzyme that phosphorylates serine and threonine residues in many

target proteins. Once thought to be a single protein, PKC is now known to comprise a large family of enzymes (isoforms) that differ in structure, cofactor requirements, and

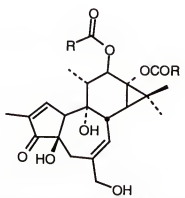


Figure 16 General Structure of Phorbol Esters

function. In addition to DAG, Protein Kinase C is also activated by a group of tumor-promoting reagents known as phorbol esters (Figure 16). These compounds bind to the same site in PKC that interacts with diacylglycerol under the same physiological conditions.

The Inhibition of Glycoside Hydrolases

Glycosidases are involved in several important biological processes, such as intestinal digestion, the biosynthesis of glycoproteins, and the lysosomal metabolism of glycoconjugates. Glycosidase inhibitors are potentially useful as antidiabetic, antiviral, antimetastatic, and immunomodulatory agents.[63] In particular, α-glucosidase inhibitors have shown potential as therapeutic agents for diabetes type 2 and HIV-1 infection.[138]

Glycosidases can be separated into two distinct mechanistic classes: those hydrolyzing the glycosidic bond with net retention of anomeric configuration, and those doing so with net inversion of anomeric configuration. Mechanisms of both classes are illustrated below (Figure 17 and 18).

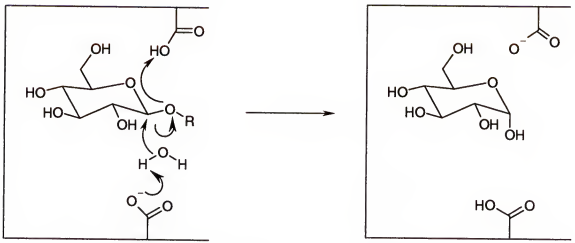


Figure 17 Inverting Glycosidase Mechanism

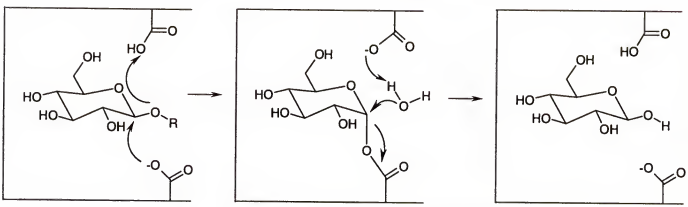


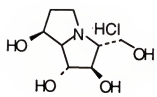
Figure 18 Retaining glycosidase Mechanism

The two mechanisms differ in that inverting glycosidases operate via a direct displacement of the leaving group by water, whereas retaining glycosidases utilize a double displacement mechanism involving a glycosyl-enzyme intermediate. Despite these differences, it is noteworthy that both classes employ a pair of carboxylic acids at the active site. With inverting enzymes, one residue acts as a general acid and the other as a general base, whereas with retaining enzymes one functions as general acid and general base while the other acts as a nucleophile and a leaving group.

Glycosidases also are divided into separate classes based on their point of cleavage. These two types of glycosidases are know as endoglycosidases and

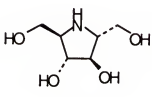
exoglycosidases. Endoglycosidases cleave glycosidic bonds within oligosaccharides, while exoglycosidases cleave one sugar at a time beginning from the non-reducing end.

Over the past few decades, one of the goals of many research chemists have been



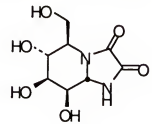
371

Australine hydrochloride
Inhibitor of amyloglucosidase



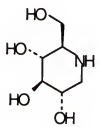
372

2,5-dideoxy-2,5-imino-D-mannitol (DMDP)
Inhibitor of invertase and glucosidase



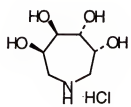
373

Kifunensine
Inhibitor of mannosidase



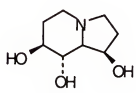
374

Deoxynojirimycin
Inhibitor of glucosidase
I and II



375

Tetrehydroxyazepane Hydrochloride
Inhibitor of β-acetylglucosaminidase



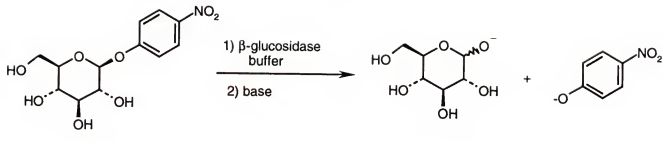
376

Castanospermine
Inhibitor of glucosidases
and some HIV function

Figure 19 Known glycosidase inhibitors

to develop sugar mimetics capable of inhibiting these enzymes. Several glycosidase inhibitors and their biological functions are shown in Figure 19.

The activity of most inhibitors against glycosidases is commonly monitored by a UV-assay. Hydrolysis of commercially available *p*-nitrophenyl glycoside by the corresponding enzyme and comparison of the rate of hydrolysis at varying inhibitor concentration allows monitoring of the inhibitors potentancy. As time elapses, *p*-nitro-



377 **378** **379**

Scheme 111

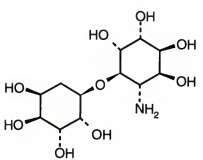
phenyl **377** is converted to its anion **378** (Scheme 111) by addition of a strongly basic buffer. This compound has a distinct color and its intensity and presence is monitored at 400 nm with a UV/VIS spectrophotometer.

CHAPTER 3
DISCUSSION

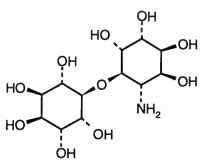
The Synthesis of *O*-Linked Cyclitol Dimer

Introduction

As shown in the preceding sections, the Hudlicky group synthesized several conduritol and inositol dimers, many having an unsubstituted methylene position. Compound **332**, in particularly displayed several interesting features, including metal-cation binding and inhibition of β-glucosidase at mM concentration. With these facts in mind, we set out to prepare amino-inositol dimer **1** (Figure 20) to study the effects of an additional oxygen substituent, on structural and biological properties as well as the ability to sequester calcium ions out of aqueous solution. It is our expectation that this molecule,



330



1

Figure 20

as well as its conduritol and acetate derivatives may show comparable biological and structural properties to previously synthesized L-*chiro*-gala-inositol dimers.

Synthesis

Introduction

The goal of this project was to synthesize *O*-Linked inositol dimer **1** and test its properties.

Retrosynthetic Analysis of the Target Molecule

Building upon the work accomplished by past members of this group[72] and taking advantage of the synthetic approach used in constructing L-*chiro*-*gala*-quercitol conjugate **332,** we set out to incorporate the same strategical approach to a new series of compounds. The basic premise of the strategy being the Lewis acid mediated opening of

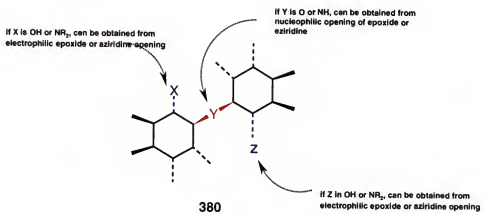

If X is OH or NR2, can be obtained from electrophilic epoxide or aziridine opening
If Y is O or NH, can be obtained from nucleophilic opening of epoxide or aziridine
X
Y
Z
If Z in OH or NR2, can be obtained from electrophilic epoxide or aziridine opening
380

Figure 21

vinyl epoxides or vinyl aziridines with a cyclic nucleophile to produce a number of cyclitol derivatives. A closer look at the structure of inositol dimer **1** shows that the oxygen or nitrogen functionality could be added in several different ways (Figure 21).

It also appears feasible to reach our target via a number of different combinations of nucleophilic and electrophilic couplings under Lewis acid conditions. If one were to

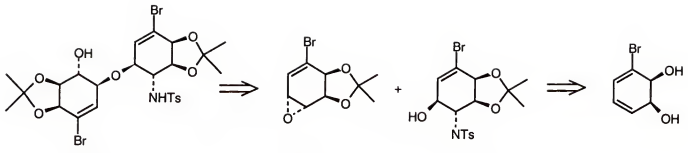


Figure 22

use the vinyl epoxide **35** as our electrophile, then a possible coupling partner would be vinyl aziridine opened alcohol **382** (Figure 22). Similarly, if we were to use vinyl aziridine **3**

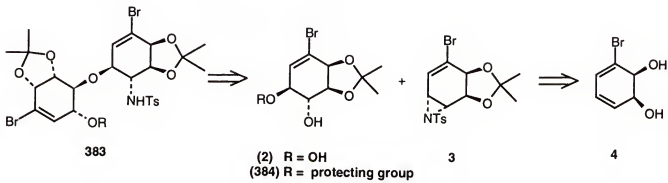
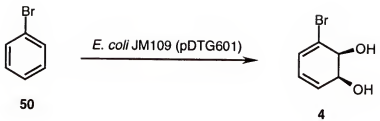


Figure 23

as our electrophile, then either *trans* diol **2** or its protected derivative **384**, both obtained from vinyl epoxide opening, should suffice as our nucleophilic coupling partner (Figure 23).

Synthesis of Diene Diol

Since the structures of the target molecules process at least two pairs of *cis*-diols, chiral diene-diol **4** should serve as a viable starting material. The biooxidation of bromobenzene (**50**) was achieved using *E.*coli. JM109 (pDTG 601), a recombinant microorganism discovered by Gibson that overexpresses the enzyme toluene



50 **4**

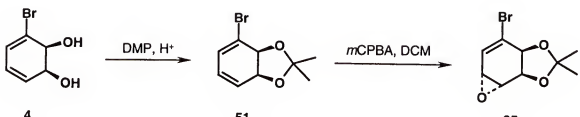
Scheme 112

dioxygenase (Scheme 112).[139] There are two phases of the microbial oxidation process: induction and production. The induction process is used to build up toluene dioxygenase. The *E. Coli.* JM109 (pDTG601) is grown overnight at 35°C in an enriched medium containing ampicillin. Iso-propyl β–D-thiogalacto-pyranoside (IPTG) (8mg/L) was added to induce the production of toluene dioxygenase by the microorganisms.

Production involves the transfer of the preculture to a 12 L fermentor containing 8L of a similar medium where the microorganism is further grown. Bromobenzene is added at a rate of 20g/hr. The metabolic transformation is monitored by observing the oxygen consumption and carbon dioxide production by the culture. Aliquots are removed from the broth, centrifuged to remove the cells, and subjected to UV analysis. Production of bromodiol can be monitored by its λ max (ca. 270nm). After all metabolic activity ceases, substrate addition is stopped and the media is neutralized to pH 7.2. This helps prevent acid-catalyzedf rearomatization of the diol. The cells are separated from the broth by centrifugation. The broth is extracted with ethyl acetate, dried with $MgSO_4$ and recrystallized from ethyl acetate/hexanes to afford (1S,2S)-3-bromocyclohexa-3,5-diene-1,2-diol **4** in a yield of 10g/L.

Synthesis of Vinyl Aziridine and Vinyl Epoxide

From *cis*-diol **4,** both vinyl aziridine **3** and vinyl epoxide **35** are obtained. Treatment of diol **4** with 2,2-dimethoxypropane, in acetone, with a catalytic amount of *p*-toluenesulfonic acid, provides acetonide **51** in quantitative yields. Epoxidation of the

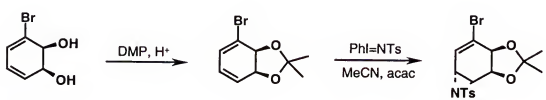


4 **51** **35**

Scheme 113

least substituted alkene with *m*-chloroperoxybenzoic acid furnishes epoxide **35** in 70% yield (Scheme 113).

Incorporating an aziridination procedure developed by Evans,[140] synthesis of aziridine **3** from acetonide **51** was achieved by using (N-tosylimino)phenyliodinane (PhI=NTs). Although not commercially available, (N-tosylimino)phenyliodinane can be prepared by reacting *p*-toluenesulfonamide and iodobenzene diacetate, with a mixture of potassium hydroxide and methanol at 0°C in the dark. The reaction is stirred for 5 hours at room temperature and the solution poured into H_2O and placed at 0°C for 18 hours. The product precipates out of solution.



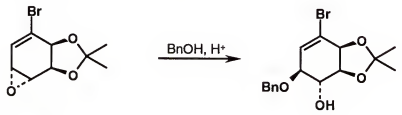
4 **51** **3**

Scheme 114

Treatment of acetonide **51** with (PhI=NTs) and cupric acetoacetate dissolved in acetonitrile gave aziridine **3** in 30% yield (Scheme 114). Although the yields are low, nearly 50% of the starting material can be recovered and the steps repeated two additional times. Several different condition variations have been attempted to increase the yields of this reaction. Efforts ranging from varying reaction temperature and reaction times to the use of different solvents, have been made. Unfortunately, all endeavors to improve this procedure were unsuccessful.

Nucleophilic Ring Opening of Epoxides and Aziridines

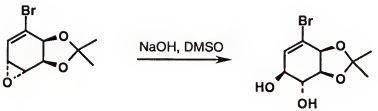
Nucleophilic ring opening of epoxide **35** was achieved under both acidic and basic conditions. Two opened epoxide adducts were synthesized and tested as viable



35 **333**

Scheme 115

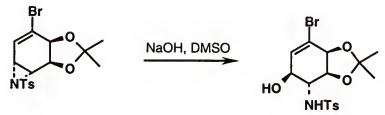
coupling partners for the synthesis of dimer **1**. Opening of epoxide **35** with benzyl alchohol in the presence of camphorsulphonic acid, afforded alcohol **333** in 58% yield



35 **2**

Scheme 116

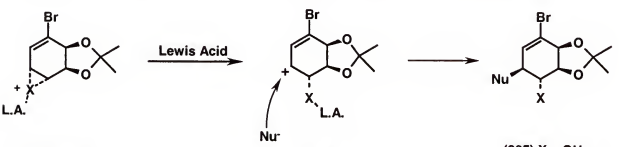
(Scheme 115), while opening of epoxide **35** with sodium hydroxide in DMSO with a catalytic amount of benzoic acid, gave *trans*-diol **2** in 52% yield (Scheme 116). The final coupling partner was obtained as aziridine **3** was opened under basic conditions, yielding alcohol **382** in 84% yield (Scheme 117).



3 **382**

Scheme 117

The nucleophilic opening of bromoepoxide **35** and bromoaziridine **3** preferentially furnish *trans*-alcohols **385** or trans-aziridines **386** respectively. Nucleophilic attack



(35) X = O
(3) X = NTs

384

(385) X = OH
(386) X = NHTs

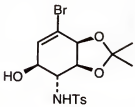
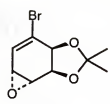
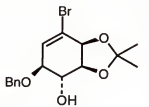
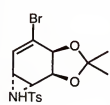
Figure 24 Possible Mechanism of electrophilic opening

occurs at the less hindered, more electropositive center. Under acidic conditions, the protonation of the epoxide/aziridine weakens the C-O/C-N bond and increases the positive charge on the vinyl carbon, which is stabilized by the inductive electron donating capability of the halogen (Figure 24).

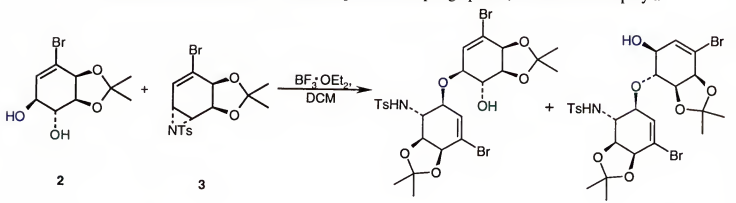
Failed Coupling Attempts

With all coupling partners synthesized, the next critical step in the process is to find a viable acid to catalyze ring opening. Attempts to couple epoxide **35** with alcohol **382** in the presence of a variety of Lewis acids at varying temperatures, failed to give the desired product. Attempts to open vinyl aziridine **3** with alcohol **333** under the same set of conditions were unsuccessful as well as illustrated in Table 1.

Table 1 Unsuccessful attempts at coupling

 **382**	 **35**	$Yb(Otf)_3$	0°C ⟶ reflux	recovered SM
		CSA	0°C ⟶ reflux	recovered SM
		BF_3OEt	0°C ⟶ reflux	decomposition of SM
		Al_2O_3	0°C ⟶ reflux	recovered SM
		SiO_2	-50°C ⟶ 0°C	recovered SM
 **333**	 **3**	$Yb(Otf)_3$	0°C ⟶ reflux	recovered SM
		CSA	0°C ⟶ reflux	recovered SM
		BF_3OEt	-50°C ⟶ 0°C	decomposition of SM
		Al_2O_3	0°C ⟶ reflux	recovered SM
		SiO_2	0°C ⟶ reflux	recovered SM

With steric hindrance as a possible variable preventing desired product formation and having explored two of the three possible coupling options, we set out to employ a

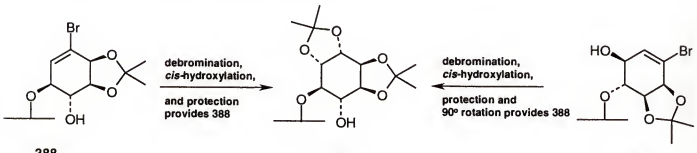


Scheme 118

third possible route. Under Lewis Acid conditions, opening of aziridine **3** with alcohol **2** in the presence of boron trifluoride diethyl ether at ⁻78°C provided dimer **381** and **387** in a 2:1 ratio as shown in Scheme 118.

Synthesis of Inositol Dimer **1**

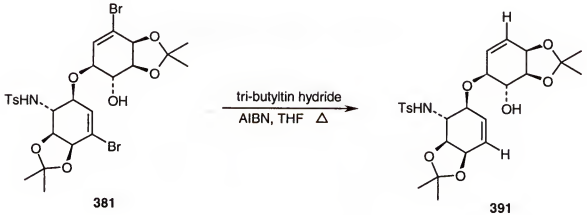
Upon closer look at isomers **381** and **387**, it was recognized that not only could our target molecule be obtained from alcohol **381**, but alcohol **387** as well. Both non-tosylated cyclitols possess a C_2 symmetry and should converge back to one compound within a few chemical manipulations (Figure 25).



388 **389** **390**

Figure 25 Possible convergent approach

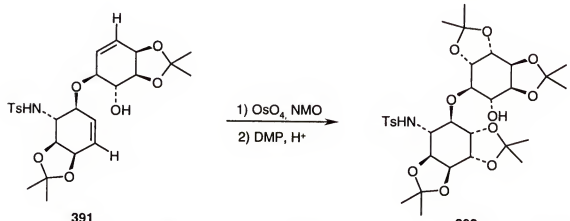
Debromination of **381** with tributyl tin hydride and AIBN afforded diene **391** in 68% yield (Scheme 119). *cis*-Hydroxylation of the resulting diene with OsO_4 and NMO



381 **391**

Scheme 119

followed by protection with 2,2-dimethoxypropane in acetone furnished tetracetonide **392** in 78% overall yield (Scheme 120). With the potential convergent molecule in hand, we

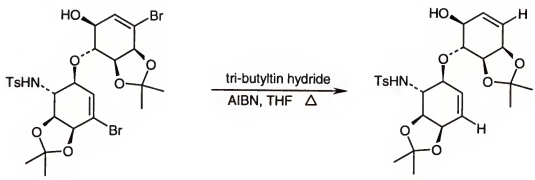


391 **392**

then attempted to synthesize this molecule from dimer **387** to see if our hypothesis proved true.

Scheme 120

Debromination of alcohol **387** with tri-butyl tin hydride and AIBN in THF, gave diene **393** in 88% yield (Scheme 121). Diene **393** was treated with OsO_4, which is

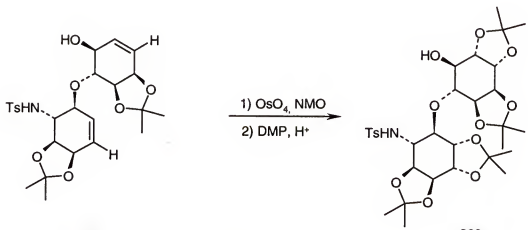


387 **393**

Scheme 121

recycled by N-methyl morpholine N-Oxide, giving a pentol which was immediately protected with 2,2-dimethoxypropane with a catalytic amount of *p*-toluenesulfonic acid,

in acetone, yielding alcohol **392** in 98% yield (Scheme 122). The melting points of each alcohol were taken individually as well as collectively to confirm that the compounds

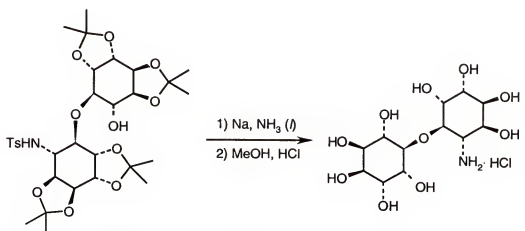


393 **392**

Scheme 122

were indeed the same. In addition to melting points, mixed NMR spectra were taken and were identical.

The synthesis of inositol dimer **1** was completed by detosylation of **392**, which was accomplished via sodium ammonia liquid reduction, followed by removal of the



392 **1**

Scheme 123

protecting groups under acidic conditions (Scheme 123). The final product was obtained in 48% yield over two steps and 8% overall yield.

Upon examining the by-products of the Lewis-acid mediated coupling, we were also able to identify compounds **394**, **395** and **396** in the reaction mixture (Figure 26).

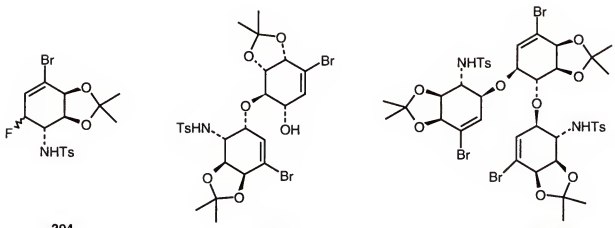


Figure 26 By-products of the $BF_3{\cdot}Et_2O$–catalyzed coupling reaction

The presence of the *cis*-configured dimer **395** was somewhat surprising and indicated that this material was formed by an S_N1-type mechanism. Surprisingly, the relative ratio of theses products (**387** : **381** : **394** : **395**: **396** = 2 : 1 : 1 : 1 : 1) proved to be generally unaffected by changes in temperature, catalyst concentration and solvent, except for a higher percentage of **394** in the reaction mixture at high catalyst concentrations.

The NMR data for compounds **381**, **387**, and **395** raise intriguing questions about the outcome of the ring opening of aziridine **3** by diol **2**. Both the ^1H-^1H vicinal couplings and the ^1H-^{13}C long range couplings confirm that **381** results from the reaction of the hydroxyl at C-3 of diol **2**, while **387** and **395** are the products of the reaction of the C-4 hydroxyl in **2**. The values of the coupling constants given in Figure 27 demonstrate

that **381** and **387** are indeed the expected products of *trans*-aziridine ring opening, but **395** strongly support a structure in which the ring opening occurred *cis* – indicative of an S_N1-like substitution of a cation or its ion pair.

The chemical shifts given in Table 2 have been determined in $CDCl_3$ at 25 °C. The chemical shifts assignment was based on ^1H-^1H couplings seen in selective decoupling experiments, and on one bond and long range ^1H-^{13}C couplings seen in GHMQC and GHMBC spectra, respectively.

The assignment of methyls of the acetonide groups was made based on the nOe's seen in the NOESY spectra, namely strong nOe's between H8 and H5, H6 and between H7' and H5', H6'. The temperature coefficients of the chemical shifts have been measured in $CDCl_3$, in the temperature interval –25 – 55 °C.

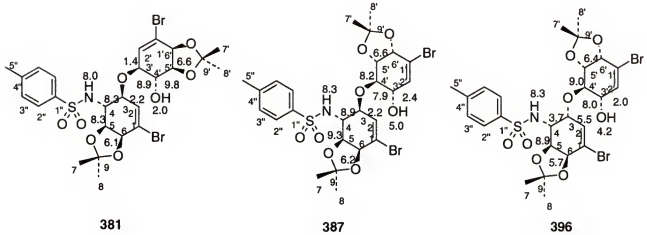


Figure 27 Position numbering and vicinal coupling constants (in Hz) for compounds **381, 387,** and **396**.

The consistency of the coupling constants $^3J_{H4\text{-}H5}$, $^3J_{H4'\text{-}H5'}$, $^3J_{H5\text{-}H6}$ and $^3J_{H5'\text{-}H6'}$ in compounds **381**, **387**, and **396** clearly demonstrates that both cyclohexene rings in all three compounds are in the same conformation, one in which the hydrogens in positions

Table 2 ^{1}H and ^{13}C chemical shifts and temperature coefficients of the ^{1}H chemical shifts for compounds **381, 387,** and **396**.

	381			**387**			**396**		
position	δ_H (ppm)	$d\delta_H/dT$ (ppb/K)	δ_C (ppm)	δ_H (ppm)	$d\delta_H/dT$ (ppb/K)	δ_C (ppm)	δ_H (ppm)	$d\delta_H/dT$ (ppb/K)	δ_C (ppm)
1	-	-	120	-	-	120.4	-	-	122.7
2	6.36	0	133.6	6.37	0.4	133.2	6.47	-0.3	132.2
3	4.15	0	77.7	3.96	2	77.5	3.92	9.7	76.2
4	3.67	0.5	57.2	3.62	0	56.7	3.53	2.3	55
5	4.07	0.5	77.1	4.15	0.4	76	4.3	-0.7	74.8
6	4.61	-0.5	77.2	4.61	0.1	77.3	4.63	-1.2	77.4
7	1.43	-0.1	27.8	1.41	0.7	27.9	1.33	-2.7	27.7
8	1.33	-0.2	26.2	1.34	0.6	26.4	1.36	-1.2	26.2
9	-	-	111.4	-	-	118.8	-	-	110.5
1'	-	-	119.2	-	-	118.4	-	-	117.8
2'	6.22	-0.1	134.3	5.98	3.4	132.7	6.26	-1.7	135.9
3'	3.97	0.5	69.3	3.8	0.9	78.3	4.12	-1.7	70.5
4'	3.44	0.8	81.4	3.48	2.7	72.7	3.18	6	83.8
5'	4.17	1.9	77.4	4.04	-0.1	77.3	4.03	1.3	77.4
6'	4.63	0.1	77.4	4.62	-0.7	77.2	4.61	-0.2	77.6
7'	1.43	0	25.9	1.57	0.4	28.4	1.39	2.7	26
8'	1.54	0	28	1.42	-0.1	26	1.39	-0.2	27.6
9'	-	-	111.2	-	-	111.4	-	-	111
OH	2.76	-5.2	-	2.6	-4.1	-	4.01	-19.3	-
NH	5.34	-6.5	-	4.76	-11	-	6.58	-19.8	-
1"	-	-	139.1	-	-	138	-	-	137.8
2"	7.83	0.2	127.7	7.78	0.6	127.4	7.84	-0.8	127.7
3"	7.29	-0.2	129.4	7.3	0	129.9	7.32	-0.8	129.9
4"	-	-	143.3	-	-	144	-	-	144.1
5"	2.42	0	21.7	2.44	0	22.2	2.42	-0.3	21.4

4,5,4',5' are pseudo-axial. Vicinal coupling constants of 8-9 Hz for the protons in positions 3', 4' and 5' in compounds **381**, **387**, and **396** confirm that these protons are all pseudo-axial. A value of ca. 2 Hz for $^{3}J_{H2'\text{-}H3'}$ also indicates that H3' is axial, a position in which the dihedral angle H2'-C2'-C3'-H3' is close to 90°. The similarity of the vicinal coupling constants on the ring originating from the aziridine in **381,** to the coupling constants on the rings originating from the diol in **381**, **387**, and **396** demonstrates that **381** is the product of *trans* ring opening, (with all of H3, H4 and H5 pseudo-axial) and that the coupling constants do not depend significantly on the substitution pattern of the ring. The values of the vicinal coupling constants of H3 in **396**, $^{3}J_{H2\text{-}H3}$ = 5.5 Hz and $^{3}J_{H3\text{-}}$

J_{H4} = 3.7 Hz, clearly demonstrate that this hydrogen is equatorial, and that **396** is the product of the *cis* ring opening. The nOe's seen in the NOESY spectrum of **396** recorded in $CDCl_3$ at –25 °C support this conclusion: H3' and H5' display the nOe expected for 1,3-diaxial protons, while H3 and H5 do not. Similarly, **381** and **387** display the nOe's between H3 and H5 and between H3' and H5'.

The NOESY spectrum of **387** indicates that the solution conformation is very similar to that observed in solid state (Figure 28). NOe's between H2 and H8', H3 and

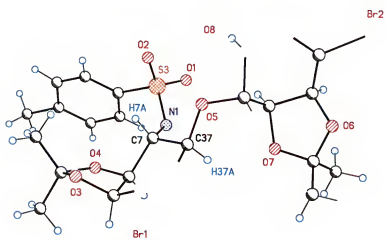


Figure 28 Crystal structure of dimer **387** as determined by X-Ray diffraction

H8', H2' and H2" demonstrate that of all the possible conformations arising from rotation about the C3-O-C4' bond, **387** adopts one in which C9' is close to C2. This is also confirmed by the nOe's of comparable size between H2 and H3 and between H2 and H4' and by a larger nOe of H4' with H2 than with H4. A larger nOe of the OH with H2 than with H2' indicates that the OH is oriented towards the tosyl group, but a small value for the temperature coefficient of the OH chemical shift suggests the lack of hydrogen bonding. A coupling constant of 7.6 Hz for the NH, together with larger nOe's to H3 and H5 than to H4, indicates that the NH is antiperiplanar to H4. The phenyl group prefers a

position on the same side of the molecule as C7, as suggested by nOe's between H2" and H7.

The NOESY spectrum of **381** in $CDCl_3$ at –15 °C displays an nOe between H2 and H4' which indicates that of all the conformations arising from rotation about the C3-O-C4' bond, **381** adopts the one in which the OH and the NH are *anti*. NOe's of a similar magnitude between H2 and H2' with H3 and H3' suggest that the bridged C3-O-C3' is twisted as to bring H3' closer to H2. Proton H2" displays nOe's with H2', H4' and H7' which confirm that the tosyl group is *anti* to the OH with respect to the C3-O-C3' junction and on the same side of the cyclohexene ring C1'-C6' as H3'. The OH displays a vicinal coupling constant of 2.0 Hz and only the nOe with H4', therefore it is most likely in one of the two gauche positions to this one. The NH has a vicinal coupling of 8.0 Hz and nOe's with H3, H4 and H5, consistent with the NH being antiperiplanar to H4. The temperature coefficients of the chemical shifts are smaller in **381** than in **396**. The protons experiencing larger values are H3, H2' and H4' – most likely the variation of the chemical shifts with the temperature is due to changes in the angle H3-C3-O-C3'-H3'. The hydroxyl proton has a small temperature coefficient, and most likely is not involved in any hydrogen bonding.

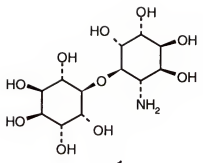
The exchangeable protons, NH and OH, display significant differences in chemical shifts, and most importantly, in the temperature coefficients of the chemical shifts between compounds **396** and **381**. Large negative temperature coefficients indicate that in **396** both of the exchangeable protons are involved in hydrogen bonding. The solvent, $CDCl_3$, is not a hydrogen bond acceptor, therefore the hydrogen bonds have to be intramolecular, and of all the conformations arising from rotation about the C3-O-C4'

bond, **381** has to adopt at low temperatures, the one in which the OH and the NH are *syn*. The NOESY spectrum of **396** at –25 °C displays the nOe's expected for such a conformation, *i.e.* H2-H7', H2-H5', OH-NH, H5-OH, NH-H3' and OH-H2".

The NH is antiperiplanar to H4 ($^3J_{NH-H4}$ = 8.0 Hz) and forms a hydrogen bond to the oxygen in the hydroxyl group, across the eight-member ring H····O-C3'-C4'-O-C3-C4-N, a picture confirmed by five large nOe's of the NH with OH, H4', H3, H4 and H5. Large nOe's of H7' with H2 and H3 agree with this hydrogen bonding, but only for the structure in which the substituents in positions 3 and 4 are *cis*. The OH proton displays a coupling of 4.2 Hz with H3' and nOe's with H2', H3' and H5 – its most likely location is interchealated between C3'-H3' and C3'-C2. The coupling constants of the OH and NH do not vary significantly with temperature, indicating that the formation of the hydrogen bond produces but a small change in the orientation of these protons relative to their vicinal partners. The nOe's of H2" with H3, H4 and H4' and the nOe of H3" with H7' they all demonstrate that the tosyl moiety is on the same side of the eight-member ring H····O-C3'-C4'-O-C3-C4-N as H4'. The protons having a large positive temperature coefficient of the chemical shifts, H3, H4, H4' and H7' are in the same region of space, which probably is the shielding region of the tosyl ring in the most stable conformation.

Molecular Structure and Calcium binding

Molecular dynamics simulations of inositol dimer **1** were obtained using Monte-Carlo simulations to find the minimum energy conformation which was optimized by semi-empirial (AM1) methods.[141] All molecular modeling input was performed by Bernhard Paul and the result is shown in the figure below.



1

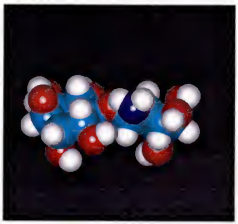


Figure 29 Molecular Modeling of dimer 1

It appears that the inositol monomers of conjugate **1** positions themselves approximately ninety degrees from one another in order to avoid steric interactions between α-substituents.

The structural arrangement of higher order oligomers of L-*chiro* and *neo*-inositols were also calculated and quite a noticeable conformational difference in the two inositols were observed. *Neo*-inositol tetramers and octomers tend to form loops while L-*chiro*-inositol oligomers preferentially conform to form helices as shown in the figure below.

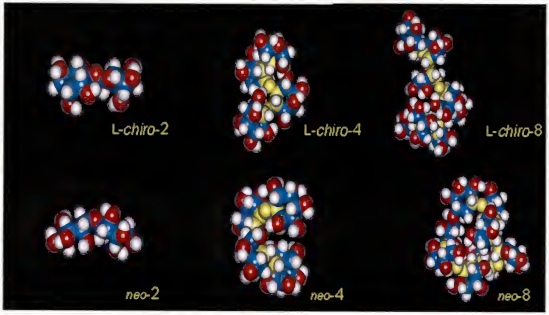


Figure 30

Slow evaporation of an aqueous solution of amine hydrochloride **1** and an equimolar aqueous solution of calcium chloride, showed no binding to calcium by the inositol conjugate.

Glycosidase Inhibition

Introduction

As with the inositol conjugates previously synthesized, we investigated the new analog's potential as a glycosidase inhibitor. The inositol dimer described in the previous section contains an extended series of hydroxyl groups, which closely resemble the three-dimensional features found in the natural sugars. Since the inositol dimer lacks the labile glycosidic bond, it should not be destroyed by a hydrolytic enzymes.

To evaluate the potential as a glycosidase inhibitor, the compound was screened against a series of hydrolases. After failed attempts with the "standard" assay described by the Molyneux lab,[142] a different method was implemented[143].

Results

To ensure the result obtained during this experiment was as accurate as possible,

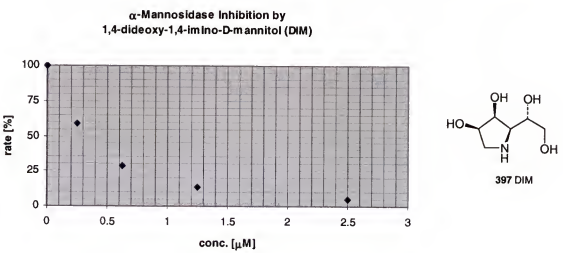


Figure 31 Inhibition of DIM

we tested the known inhibitor 1,4-diamino-1,4-dideoxy-D-mannitol (DIM) (Figure 31).

The IC_{50} of tetrol **397** is reported at a substrate concentration of .33 mM at pH 4.5 to be .5 μM. In our assay, for a substrate concentration at 2.5 mM and a pH of 6.0, DIM possessed an IC_{50} of .35 μM, which is in good agreement with the reported value.

With the modified assay yielding acceptable results, we set out to investigate the inhibition potential of inositol dimer **1**. The results are given below.

The oxygen-linked amino-inositol dimer **1** (Figure 32) proved to be a moderate

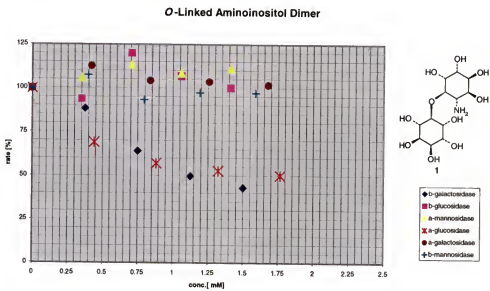


Figure 32 Inhibition by *O*-linked dimer **1**

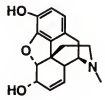
inhibitor of both, β-galactosidase (IC_{50} ~ 1.1 mM) and α-glucosidase (IC_{50} ~ 1.7 mM).

CHAPTER 4
AUXILIARY REPORT

Introduction

After the successful synthesis of amino inositol dimer **1**, we then turned our attention towards an approach to the morphine skeleton. The morphine alkaloids are of considerable pharmacological interest due to their potent analgesic properties.[144] In recent years morphine has been used as an anesthetic in open-heart surgery mainly because of its ability to slow down respiratory activity without affecting cardiac function.

Although interest of synthetic chemists in morphine dates back to the 1950's, it continues unabated to this day. There still remains a desire to develop a method to construct the relatively small alkaloid consisting of three carbocycles and two



Morphine (398)

Figure 33

heterocyclic rings in a manner that competes with its isolation. The next section of this report discusses an attempt to synthesize thiebaine via two Diels-Alder approaches.

Retrosynthetic Approach

We envisioned obtaining the target, by either route with inexpensive and commercially available starting material. The first approach would begin with iodothiophene (**399**), which upon conversion to its methoxy analog followed by formalyation would provide 5-methoxy-2-carboxaldehyde (**400**) (Figure 34). McMurry coupling of this aldehyde should provide alkene **401**. Hydroboration followed oxidation of the two thiophene rings should give bis-thiophene 1,1 dioxide **402**. PCC oxidation of **402** followed by reductive amination should give secondary amine **403**. DCC coupling

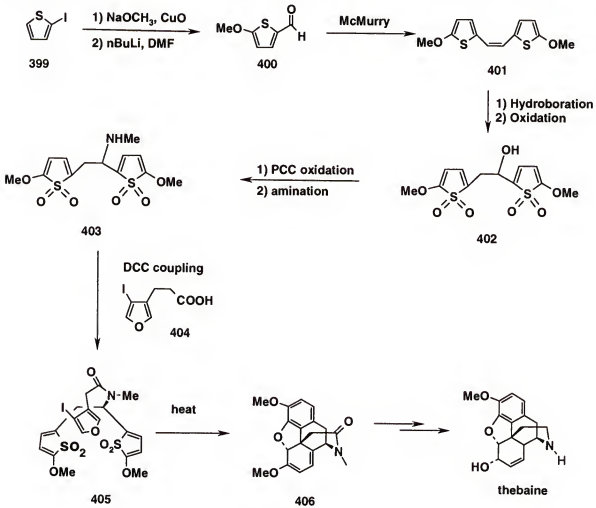


Figure 34

involving aldehyde **404** should give the intermediate **405** for consecutive Diels-Alder cycloadditions. Heating of **405** at elevated temperatures should afford the cyclized adduct **406** which would be further transformed to thebaine, thus formalizing a synthesis of Morphine (**398**).

The second approach begins with gluconolactone (**407**), which when heated in the presence of acetic anhydride should give pyrone **408** (Figure 35). Deacylation, followed

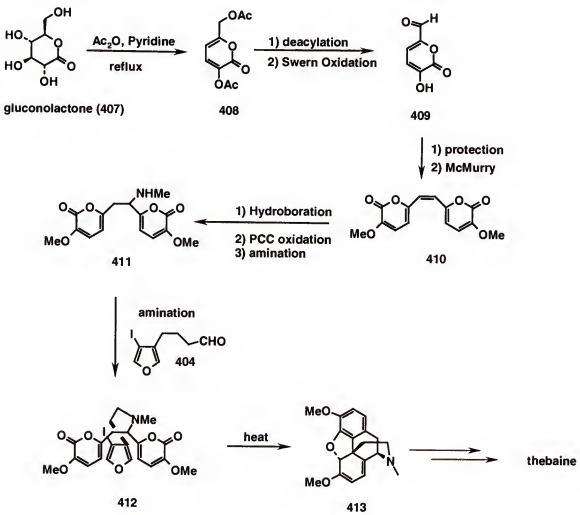


Figure 35

by oxidation of the primary alcohol should afford aldehyde **409**. Protection of the free alcohol and subjection of the aldehyde to McMurry conditions should provide alkene

410. Amine **411** should be obtained in a fashion similar to that of compound **402**, via hydroboration fol-lowed by oxidation and amination. A second amination involving aldehyde **404** would give tertiary amine **412**. We anticipate that heating compound **412** would give cycloadduct **413**, which upon further manipulation will give thebaine, thus formalizing a second route to Morphine.

Results

Our research efforts began with two independent model studies.

Thiophene 1,1 dioxides have been shown to undergo Diels-Alder reactions with a variety of dienophiles[145]. We set out to synthesize vinyl alkene **416** to see if its possible to oxidize thiophene in the presence of an alkene (Figure 36).

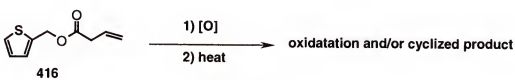
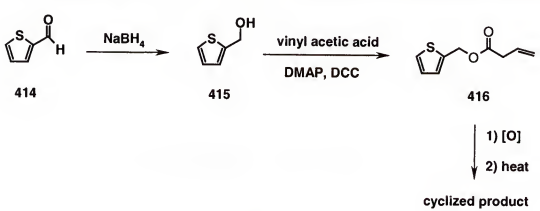


Figure 36

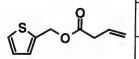
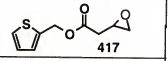
Reduction of commercially available 2-thiophene carboxaldehyde with sodium borohydride gave alcohol **415** in 87% yield (Scheme 124). DCC coupling of **415** with



Scheme 124

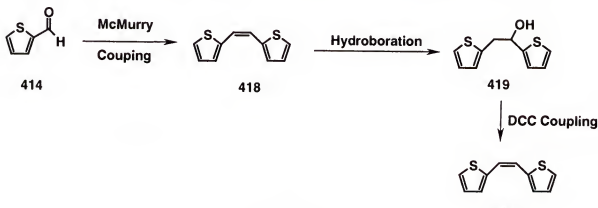
vinyl acetic acid, gave vinyl ester **416** in 84% yield. Oxidation[146] of this compound in the presence of several oxidants did not yield the sulphone, sulfoxide, or cycloaddition product (Table 3).

Table 3 Results of **416** oxidation

	oxidant	conditions	results
 **416**	*m*CPBA, CH_2Cl_2	reflux	 **417**
	30%, H_2O_2 AcOH	100°C	SM recovered
	$NaIO_4$, H_2O EtOH	reflux	decomposition of SM
	Oxone	Room Temperature	SM recovered
	$NaBO_4 \cdot 10H_2O$	50°C 96 hr.	decomposition of SM

A model of the dimeric compound was also attempted (Scheme 125).

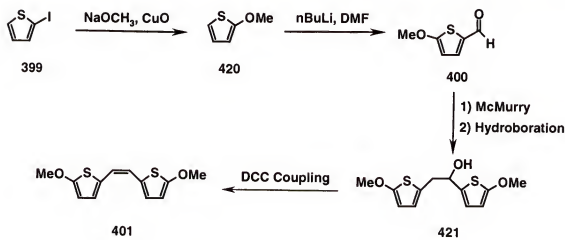
McMurry coupling of **414** afforded alkene **418** in 42% yield. Hydroboration of **418** gave alcohol **419** in 89% yield. DCC coupling of **419** with vinyl acetic acid gave



Scheme 125

only the previously synthesized alkene via elimination. We then turned our attention to the construction of the 2,5 substituted derivative to see if more favorable results were obtainable.

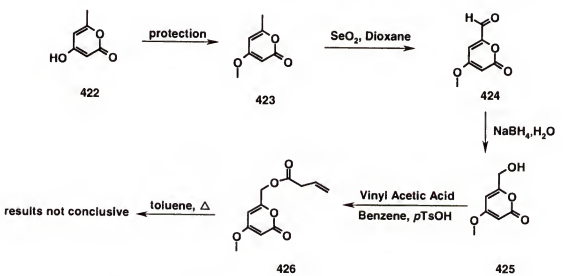
2-Methoxythiophene (**420**) was obtained by a copper-catalyzed Williamson synthesis from commercially available iodothiophene (**399**) (Scheme 126). Formylation



Scheme 126

of **420** gave aldehyde **400** in 78% yield. McMurry coupling of **400** followed by hydroboration provide alcohol **421**. Again any attempts to couple vinyl acetic acid with this compound failed.

The pyrone model study began with commercially available 2-methyl-4-hydroxy (**422**) pyrone which after methylation gave compound **423** in 89% yield (Scheme 127).



Scheme 127

Oxidation of the methyl group with selenium dioxide gave aldehyde **424** in 65% yield. Reduction of **424** with sodium borohydride gave alcohol **425** in 48% yield. Coupling of **425** with vinyl acetic acid in benzene gave vinyl ester **426** in 54% yield. Heating of pyrone **426** in toluene at elevated temperatures gave a compound, which was not characterized, and attempts to repeat this procedure failed.

CHAPTER 5
CONCLUSION

In the first part of this dissertation, a chemoenzymatic approach to oxygen-linked amino-inositol dimer was achieved. *cis*-Bromocyclohexadiene-diol, obtained from whole-cell fermentation of bromobenzene with *E.* coli JM109 (pDTG601), was used as our homo-chiral starting material in the synthesis of all compounds. Opening of vinyl epoxides and aziridines under Lewis acid conditions, the same strategy employed in the synthesis of L-*chiro*-gala-conjugate, afforded the target molecule. Because of the inherent C_2 symmetry of inositol dimer **1**, a convergent route could be incorporated into the synthesis.

In addition to inositol dimer **1**, several other conjugates were synthesized and tested for their potential as glycosidase inhibitors.[147] All dimers were evaluated in to glycosidase inhibition studies. Of the six commercially available glycosidases chosen for testing, two were inhibited by the newly prepared dimers. The reason for this remains unclear, since the hydroxylation patterns found in these sugars do not match the ones possessed by the dimers.

Three-dimensional analyses of all compounds were performed. Molecular modeling of the target molecules and higher order oligomers provided further insight into the spatial arrangement of these compounds. It appears that higher oligomers of L-*chiro* inositols tend to form helices, while oligomers of *neo*-inositols preferentially conform into loops.

In the latter portion of the document, attempts to cyclized pyrone **425** as well as oxidize and cyclized any of the thiophene compounds synthesized were unsuccessful. Both thiophene 1,1-dioxides and pyrones have been shown to undergo Diels-Alder cycloadditions but in these particular instances, this was not the case.

In our first model study, oxidation of vinyl ester **415** provided only epoxide **416** in less than 10% yields. It appears that the alkene reacts faster than the sulfur of thiophene. In the case of the dimeric thiophene model, oxidation was not achieved, as well. It has been shown that 2,5-substituted thiophenes tend to be more readily oxidized than mono substituted derivatives. The inability to synthesize a cycloaddition intermediate in thiophene project left this question unanswered.

In the pyrone model study, although we were able to construct the Diel-Alder intermediate, we were unable to achieve cyclization. It has been shown that there is a difference of reactivity based on the substitution pattern of the pyrone itself. 2-pyrones with a substituent at the 3 or 5 position tend to react faster than the 4-substituted 2-pyrone.[148] Chen and Liao reported that attempts to cyclize 2, 5-substitued pyrones were accomplished with furans, but they were unable to achieve the same cyclization with the 2,4-substituted derivative. This may help explain one contributing factor to the demise of this project.

CHAPTER 6
EXPERIMENTAL

All non-aqueous reactions were performed using standard techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride, whereas ether ethyl and THF were dried over sodium/ benzophenone. Thin-layer chromatography was performed on Silicycle plates and flash chromatography using Natland 200-400 mesh silica gel. Melting points were recorded on Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR or on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz), a Varian VXR (300 MHz), or a Mercury 300 (300 MHz) instrument. All chemical shifts are referenced to TMS or residual undeuterated solvent. For ^{13}C-NMR spectra in D_2O, a small amount of MeOH was deliberately added as internal standard. Optical rotation was measured on a Perkin Elmer 341 instrument. All combustion analyses were performed by Atlantic Microlab, Norcross GA. Mass spectra were recorded by the analytical division at the University of Florida, Gainesville.

General procedure for the inhibition assays

All measurements were made on a Perkin Elmer 8452A diode array spectrophotometer with a multi-cell attachment.

The following buffers were used for the tests:

Sodium phosphate buffer (25 mM) pH=7.3 for β-galactosidase

Sodium phosphate buffer (25 mM) pH=6.8 for β-glucosidase, α-glucosidase

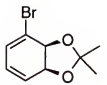
Sodium phosphate buffer (25 mM) pH=6.0 for α-mannosidase, α-galactosidase

Sodium phosphate buffer (25 mM) pH=5.5 for β-mannosidase

The inhibitor concentration was kept around 1 mg/mL. All tests were run at 37°C, except for the α-mannosidase test, which was performed at 25°C. The substrate concentration was 5 mM except for the α- and β-mannosidase assay were it was 2.5 mM. The enzyme concentration was adjusted to produce a slope of about 0.02-0.025 except for the β-mannosidase assay, were it was adjusted to give a slope of 0.005-0.01. The final volume (adjusted with the corresponding buffer) was 1000 μL in all cases.

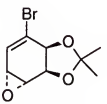
To a solution of varying amounts of inhibitor (usually 0-400 mL) in the corresponding buffer solution was added 100 μL of the enzyme solution, except for one vial that was run as a blank to correct for the autohydrolysis of the substrate. All samples were pre-incubated at the corresponding temperature for 30 minutes, after which the reaction was started by addition of the substrate (400 μL). The absorption was then recorded over a period of 20 minutes by continually scanning all samples. The slopes obtained for the individual samples were then plotted against the inhibitor concentration to obtain the usual inhibition curves.

(2S,3S)-2,3-O-Isopropylidene-1-bromocyclohexa-4,6-diene (51).



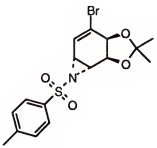
To a solution of diene diol **4** (700 mg, 3.66mmol), dissolved in 20 ml of acetone, was added 2,2-dimethoxypropane (1ml), followed by a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 45 minutes To the mixture was added CH_2Cl_2 followed by 5 ml of saturated $NaHCO_3$, and stirring was continued 10 minutes. The reaction mixture was diluted with 10 ml of ethyl acetate, and the aqueous layer was washed with ethyl acetate (3 x 20ml). The organic layer was washed with brine (3 x 10ml). The organic extracts were dried over magnesium sulfate, and the solvent was evaporated, yielding 807 mg (95%) of a yellow oil. The following data, each checked against previously reported literature data, was used to identify the compound: R_f, ^1H NMR, ^{13}C NMR.[149]

(1R,4S,5S,6R)-3-bromo-4,5-O-isopropylidiene-7-oxabicyclo[4.1.0] hept-2-ene-4,5-diol (35) .



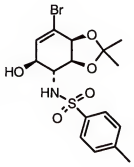
To a solution of acetonide **51** (500 mg, 2.15mmol) in CH_2Cl_2 (20ml) was added *m*CPBA (600 mg, 3.84 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane : ethyl acetate 4:1) to afford (370 mg, 70%) of white crystals. The following data, each checked against previously reported literature data, was used to identify the compound: R_f, ^1H NMR, ^{13}C NMR, m.p.[151]

(1R,4S,5S,6R)-3-Bromo-4,5-(isopropylidenedioxy)7-(4-methy-ylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (3)



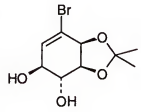
To an ice bath cooled solution of $Cu(acac)_2$ (0.670, 2.6 mmol) *p*-(tosylimino)phenyliodane (4.80g, 12.8 mmol) in CH_3CN was added (12,2S)-3-bromo-1,2-(isopropylidenedioxy) cyclohexa-3,5-diene(5.95g, 25.7 mmol) dissolved in CH_3CN. The mixture was stirred at room temperature for 3h. and filtered through a pad of celite. The solvent was removed in vacuo and the crude product recrystallized as a white from hexane/ethyl acetate yielding 5.96g (58%) of **3**. mp = 203-206 °C (lit.[150] mp = 206-207).

N-(7-Bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide(382)



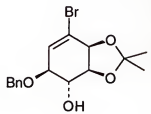
To a solution of aziridine (0.800g, 2.2 mmol) in CH_2Cl_2/dioxane mixture (1:1) was added H_2O and sodium benzoate. The resulting mixture was refluxed for 4hrs. The mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 x 10ml). The solution was then dried with $MgSO_4$, and the solvent was removed under reduced pressure. The substrate was obtained by recrystallization (Hex:CH_2Cl_2) (530mg, 68%); Rf = .2 hexanes: ethyl acetate 3:1; mp: 153-155°C; $[\alpha]_D^{20}$ –25.0 (c 1.0, $CHCl_3$) δ: 7.78 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.24 (d, J = 3.3 Hz, 1H), 4.83 (d, J = 5.7 Hz, 1H), 4.57 (d, 5.4 Hz, 1H), 4.16 (d, 7.2, 6.0 Hz, 1H), 3.97 (t, 5.7, 3.0 Hz, 1H), 3.87 (dd, J = 5.1, 2.4 Hz, 1H), 3.30 (dt, 13.8, 6.5 Hz, 1H), 2.41 (s, 1H), 1.56 (s,3H), 1.28 (s, 3H); ^{13}C ($CDCl_3$) δ: 144.16, 135.78, 134.04, 128.81, 127.54, 120.52, 112.05, 111.30, 76.27, 75.76, 69.97, 56.63, 27.16, 25.93, 21.53; IR (KBr/cm^{-1}): 3403, 2980, 1385, 1375, 1226, 1066, 982; HRMS Calcd. for $C_{16},H_{20},BrNO_5S$ (M+): 418.31; Found 418.03; Anal. Calcd. for $C_{16},H_{20},BrNO_5S$: c, 45.94; H, 4.82; Found C, 46.16, H 4.79.

(1S,2R,3S,4S)-5-Bromo-3,4-O-isopropylidenexyxlohex-5-ene-1,2,3,4-tetraol (2)



To an ice-cooled solution of (1R,4S,5S,6R)-3-bromo-4,5-O-isopropylidene-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol **35** (2.25, 9.0 mmol) in DMSO (5 ml) was added aqueous 10% KOH (5ml). The mixture was refluxed for 6 h. The aqueous solution was extracted with ethyl acetate (6 x 6ml). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by flash chromatography (10% H_2O silica gel;ethyl acetate-hexane 3:1) to afford 982 mgs of diol **2** (41%) which was recrystallized from CH_2Cl_2-hexane: R_f = .38 (ethyl acetate-hexane 4:1), m.p. 145 °C (lit.[151] m.p. 147 °C).

5-benzyloxy-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol (333)

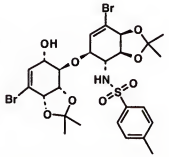


To a flame dried flask was added epoxide **35** (0.200g, 0.08mmol) dissolved in anhydrous CH_2Cl_2. The solution was cooled with an ice bath to 0°C. To the mixture was added BnOH (0.174g, 1.6mmol) followed by camphorsulfonic acid (.037g, 0.16 mmol) and the solution was warmed to room temperature for 2h. The solvent was removed in vacuo and the mixture separated via flash chromatography (hexanes:ethyl acetate 5:1). 2.11 g (74%) of a white solid was obtained. ^{1}H NMR of this compound matched the literature reported data.[133]

Aziridine-Alcohol Couplings; Typical procedure:

Borontrifluoride-diethyl ether complex (24.7 μL, 250 μmol) in dry CH_2Cl_2 (15 mL) was added to a stirred solution of aziridine **3** (1.0 g; 2.50 mmol) and diol **2** (0.66 g; 2.50 mmol) at $-50^{\circ}C$. The mixture was allowed to warm up to $-10^{\circ}C$ and stirred at that temperature for 20 minutes. A saturated solution of $NaHCO_3$ (20 mL) was added and mixture was extracted with CH_2Cl_2 (3x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The products of the reaction (**381**, **387**, **394**, **395**, and **396**) were separated by flash chromatography (3:1 hexanes: ethyl acetate)

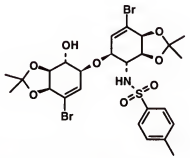
N-[7-Bromo-5-(7-bromo-4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yloxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (387)



mp = 131-133°C; $[\alpha]_D^{25}$ = +47.4 (c = 1.0, $CHCl_3$);

IR (KBr pellet) 3480, 3272, 2987, 1495, 1382, 1247, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.36 (d, *J* = 1.8 Hz, 1H), 6.22 (d, *J* = 2.1 Hz, 1H), 5.34 (d, *J* = 7.2 Hz), 4.63 (dd, *J* = 5.7, 5.4, 2H), 4.17 (dd, *J* = 8.1, 7.5 Hz, 2H), 4.07 (dd, *J* = 8.9, 8.4 Hz, 1H), 3.97 (m, 1H), 3.67 (m, 1H), 3.44 (dd, J = 8.1, 7.5 Hz, 1H), 2.76 (bs, 1H), 2.42 (s, 3H), 1.54 (s, 3H), 1.43 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.3, 139.1, 134.3, 133.6, 129.4, 127.7, 120.0, 119.2, 111.4, 111.2, 81.4, 77.7, 77.4, 77.4, 77.2, 77.1, 69.3, 57.2, 28.0, 27.8, 26.2, 25.9, 21.7; HRMS calcd. for $C_{25}H_{32}Br_2NO_8S$ $(M+H)^+$: 664.0215; Found 664.0213; Anal. Calcd. for $C_{25}H_{31}Br_2NO_8S$: C, 45.13; H, 4.70. Found C, 45.08, H, 4.88.

N-[7-Bromo-5-(7-bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yloxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (381)



mp = 224-225°C; $[\alpha]_D^{25}$ = +64.9 (c = 1.0, $CHCl_3$);

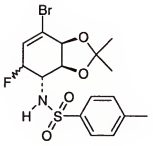
IR (KBr pellet) 3469, 3260, 2987, 2932, 1454, 1382,

1219, 1076 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H),

6.34 (s, 1H), 5.92 (s, 1H), 4.58 (dd, *J* = 5.4, 4.8 Hz, 2H), 4.12 (dd, *J* = 8.1, 6.3 Hz, 1H), 4.01 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.94 (d, *J* = 7.2 Hz, 1H), 3.76 (d, *J* = 8.4 Hz, 1H), 3.58 (dd, *J* = 8.1 Hz, 2H), 3.42 (dd, *J* = 8.7 Hz, 1H), 2.62 (bs, 1H), 2.41 (s, 3H), 1.54 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 144.0, 138.0, 133.2, 132.7, 129.9, 127.4, 120.4, 118.8, 118.4, 111.4, 78.3, 77.5, 77.3, 77.3, 77.2, 56.7, 28.4, 27.9, 26.4, 26.0, 22.2; HRMS calcd. for $C_{25}H_{32}Br_2NO_8S$ $(M+H)^+$: 664.0215; Found 664.0216; Anal. Calcd. for $C_{25}H_{31}Br_2NO_8S$: C, 45.13; H, 4.70. Found C, 45.00, H, 4.63.

N-(7-Bromo-5-fluoro-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (394)



mp = 98-99°C; $[\alpha]_D^{25}$ = +64.9 (c = 1.0, $CHCl_3$);

IR (KBr pellet) 2980, 2922, 1433, 1355,

1201, 1089 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.98 (d, *J* = 2.4 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H),

6.48 (dd,J = 6.9, 3.9 Hz, 1H), 5.29 (m, 1H), 5.12

(m, 1H), 4.87 (m, 1H), 4.66 (m, 1H), 3.92 (m, 1H), 2.62 (s, 3H), 2.62 (s, 3H), 1.54 (s 3H),

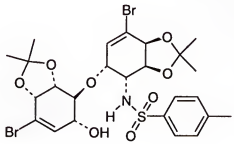
1.39 (s, 3H), ^{13}C NMR ($CDCl_3$ 75 MHz) δ 143.9, 136.3, 129.7, 129.5, 127.7, 127.4,

110.8, 86.4, 84.1, 74.7, 53.4, 27.2, 25.9, 21.5; HRMS calcd. for $C_{16}H_{19}BrNO_4SF$ $(M+H)^+$:

420.0280; Found 422.026; Anal. Calcd. for $C_{16}H_{19}BrNO_4SF$: C, 45.72; H, 4.56. Found

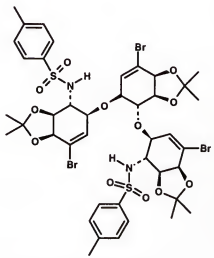
C, 45.59, H, 4.59.

N-[7-Bromo-5-(7-bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yloxy)-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (395)



mp = 128-129°C; $[\alpha]_D^{25}$ = +47.4 (c = 1.0, $CHCl_3$); IR (KBr pellet) 3460, 3255, 2968, 1487, 1390, 1240, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 6.58, 6.26, (s, 1H), 4.63 (dd, *J* = 5.4, 4.8 Hz, 2H), 4.30, 4.12 (dd, *J* = 8.1, 6.3 Hz, 1H), 4.03, 4.01 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.92, 3.53 (d, *J* = 7.2 Hz, 1H), 3.18 (d, *J* = 8.4 Hz, 1H), 2.42 (s, 3H), 1.39 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 144.1, 137.8, 135.9, 132.2, 129.9, 127.7, 122.7, 83.8, 77.6, 77.4, 77.2, 76.2, 74.8, 70.5, 55.0, 27.7, 27.6. 26.0, 21.4; HRMS calcd. for $C_{25}H_{32}Br_2NO_8S$ $(M+H)^+$: 664.0215; Found 664.0213; Anal. Calcd. for $C_{25}H_{31}Br_2NO_8S$: C, 45.13; H, 4.70. Found C, 45.08, H, 4.88.

N-(7-Bromo-5-[7-bromo-4-(2,2,dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yloxy)-2,2,dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]4-methyl-benzenzesulfonamide-4-(2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenzesulfonamide (396)



mp = 126-127°C; $[\alpha]_D^{25}$ = +33.9 (c = 1.0, $CHCl_3$);

IR (KBr pellet) 2981, 2902, 1460, 1352,

1245, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz)

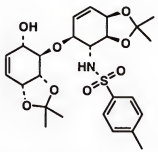
δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H),

7.29 , (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H),

6.23 (d, *J* = 2.2, 1.7 Hz, 2H), 6.01 (d, *J* = 1.8 Hz, 1H),

5.85 (d, *J* = 8.5 Hz, 1H), 5.58 (d, *J* = 7.1 Hz, 1H), , 4.64 (d, *J* = 6.0 Hz, 2H), 4.50 (d, *J* = 6.6 Hz, 1H), 4.20 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.06 (dd, *J* = 9.6, 6.1 Hz, 1H), 3.95 (dd, *J* = 9.8, 8.2 Hz, 2H), 3.85 (dd, *J* = 8.3, 6.6 Hz, 1H), 3.55 (m, 2H), 3.04 (t, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H) , 1.36 (s, 3H), 1.35 (s, 3H), ^{13}C NMR ($CDCl_3$ 75 MHz) δ 143.6, 143.3, 138.9, 133.7, 133.6, 132.9, 120.5, 118.7. 111.6, 111.4, 111.3, 79.8, 78.2, 77.8, 77.4, 77.2, 77.1, 77.1, 28.2, 28.0, 27.9, 26.9, 26.3, 25.8, 22.0, 21.8;HRMS calcd. for $C_{41}H_{49}Br_2N_2O_{12}S_2$ $(M+H)^+$: 1065.693; Found 1065.0338; Anal. Calcd. for $C_{41}H_{49}Br_2N_2O_{12}S_2$: C, 46.21; H, 4.63. Found C, 45.37, H, 4.61.

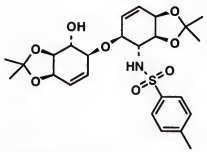
N-[5-(4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yloxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (393)



A degassed solution of alcohol **387** (780 mg, 1.1 mmol) in THF (20 mL), was added tributyltin hydride (1.27 mL, 4.7 mmol) and the solution heated to reflux for 1 hour. To the mixture was then added AIBN (19 mg, 0.011 mmol) and the solution continued to reflux for 12 hours. The solvent was removed under reduced pressure and the residue purified by flash chromatography (3:1 hexane: ethyl acetate) to give diene **393** (551 mg, 92%) as a white solid.

mp = 198-199 °C; $[\alpha]_D^{25}$ = +27.6 (c = 1.0, $CHCl_3$); IR (KBr pellet) 3504, 3204, 2983, 1599, 1287, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.04 (d, *J* = 9.9 Hz, 2H), 5.87-5.77 (m, 2H), 5.55 (d, *J* = 6.9 Hz, 1H), 4.57 (s, 2H), 4.19 (d, *J* = 9.9, 1H), 4.05-3.90 (m, 4H), 3.62 (dd, *J* = 16.8 Hz, 1H), 3.30 (dd, *J* = 8.7 Hz, 1H), 2.51 (d, *J* = 3.3 Hz, 1H), 2.40 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H); 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 142.6, 139.4, 133.2, 133.1, 128.9, 127.4, 110.5, 110.3, 82.6, 77.0,76.5, 72.9, 72.2, 68.5, 58.0, 27.8, 27.6, 25.9, 25.4, 21.3; HRMS Calcd. for C_{25},H_{34},NO_8S $(M+H)^+$: 508.2005, Found 508.2006; Anal. Calcd. for $C_{25}H_{33}NO_8S$: C, 59.16; H, 6.55. Found C, 59.06; H, 6.44.

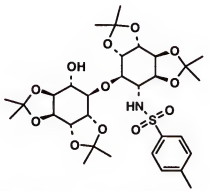
N-[5-(5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yloxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (391)



Procedure analogous to the preparation of **393**.

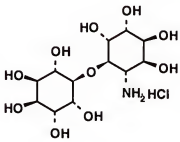
Diene **391** (86 %) was obtained as a white solid. mp = 218-225 °C (decomp); $[\alpha]_D^{25}$ = +15.6 (c = 1.0, $CHCl_3$); IR (KBr pellet) 3516, 3212, 2984, 1618, 1247, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 9.9 Hz, 1H), 5.87 (d, *J* = 8.1 Hz, 1H), 5.68 (s, 2H), 5.00 (d, *J* = 7.5 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.09-3.03 (m, 3H), 3.85 (d, *J* = 8.7 Hz, 1H), 3.52-3.37 (m, 2H), 2.60 (bs, 1H), 2.38 (s, 3H), 1.51 (s, 3H), 1.35 (d, *J* = 3.6 Hz, 6H); 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 Hz), δ 142.6, 139.4, 133.2, 133.1, 128.9, 127.4, 110.5, 110.3, 82.6, 77.0,76.5, 72.9, 72.2, 68.5, 58.0, 27.8, 27.6, 25.9, 25.4, 21.3; HRMS Calcd. for $C_{25}H_{34}NO_8S$ $(M+H)^+$: 508.2005, Found 508.1969; Anal. Calcd. for $C_{25}H_{33}NO_8S$: C, 59.16; H, 6.55. Found C, 59.12, H, 6.48.

N-[5-(5-Hydroxy-2,2,7,7-tetramethyl-hexahydro-benzo[1,2-d;3,4-d]bis[1,3]dioxol-4-yloxy)-2,2,7,7-tetramethyl-hexahydro-benzo[1,2-d;3,4-d]bis[1,3]dioxol-4-yl]-4-methyl-benzenesulfonamide (392)



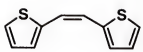
To a solution of diene **391** (213 mg, 0.42 mmol) in a 10:1 mixture of acetone and water (10 mL), was added NMNO (295 mg, 2.5 mmol). A crystal of solid OsO_4 was added and the reaction mixture was stirred overnight. The reaction was quenched with excess sodium sulfite and stirring was continued for 15 minutes. The pH was adjusted to 3 with 1N HCl (10 mL) and the mixture extracted (10 x 20 mL) with CH_2Cl_2. The combined organic layers were dried with $NaSO_4$ and concentrated *in vacuo* to yield a brown solid. The crude mixture was dissolved in acetone (10 mL) and DMP (0.11mL, 0.90 mmol) was added, followed by a catalytic amount of *p*TsOH. The solution was stirred at room temperature for 4 hrs. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% NaOH (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), dried with $MgSO_4$, and the solvent removed under reduced pressure. Flash chromatography gave **392** (178 mg; 65% for two steps). mp = 198-199 °C; $[\alpha]_D^{25}$ = –44.6 (c = 1.0, $CHCl_3$); IR (KBr pellet) 3449, 2990, 2937, 1495, 1374, 1217, 1054, 858, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 4.4 Hz, 1H), 4.31 (m, 3H), 4.17 (m, 3H), 4.11 (m, 3H), 4.02 (dd, *J* = 7.4, 6.5 Hz, 1H), 3.49-3.25 (m, 4H), 2.41 (s, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 137.8, 129.1, 127.6, 110.1, 110.0, 109.5, 85.4, 80.3, 79.0, 78.5, 78.3, 77.6, 76.1, 75.5, 71.9, 56.7, 27.7, 27.5, 27.1, 26.1, 25.4, 25.2, 25.1, 24.7, 21.4; HRMS Calcd. for $C_{31}H_{46}NO_{12}S$ $(M+H)^+$: 656.2740; Found 656.2748; Anal. Calcd. for $C_{31}H_{45}NO_{12}S$: C, 56.78; H, 6.92. Found C, 56.66, H, 6.78.

6-(2,3,4,5-Tetrahydroxy-6-methyl-cyclohexyoxy)-cyclohexane-1,2,3,4,5-pentaol (1)



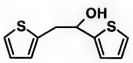
A flame dried round bottom flask, was charged with sodium pieces (12 mg, 0.05 mmol) under argon. Liquid ammonia was bubbled through and liquefied *via* a cold finger. A solution of **392** (120 mg, 0.01 mmol) dissolved in THF (3 mL) was added dropwise, allowed to stir for 5 minutes, and opened up to air to release the remaining ammonia. Water (5mL) was added slowly to quench the excess sodium and the mixture was extracted with diethyl ether (3x 10ml). The solution was dried with sodium sulfate and the solvent removed under reduced pressure to give a brown oil. The crude residue was dissolved in methanol (5 mL). Two drops of concentrated hydrochloric acid was added and the solution left to stand for 24 hours. A white precipitate formed, which was removed by filtration and washed with MeOH (10 ml). The white solid was recrystallized from MeOH and ether to yield the title compound (39 mg; 52% over 2 steps). $[\alpha]_D^{30}$ = -72.8 (c=1.0, H_2O); IR (KBr-pellet) 3444, 2932, 1567, 1420, 1375, 1320, 1210, 1085, 900 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.18-3.91 (m, 8H), 3.82-3.77 (m, 3H), 3.42 (dd, *J* = 10.2 Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 87.2, 83.1, 75.6, 74.3, 74.1, 74.0, 73.7, 73.6, 73.3, 72.9, 69.9, 57.9; HRMS calcd. for $C_{12}H_{24}NO_{10}$ (M+): 342.1400; Found: 324.1402; Anal. Calcd. for $C_{12}H_{23}NO_{10} \cdot 0.5HCl \cdot 0.5H_2O$: C, 39.11; H, 6.70; Found C, 38.67, H, 6.79.

E-1,2-di-2-thienylethylene (418)



To a stirred solution of thiophene-2-carbaldehyde (8.64, 77.0 mmol) in THF was added titanium (IV) chloride (34.6g, 230 mmol) over a period of 0.5 h at 0°C. After stirring at this temperature for 0.5 h, zinc powder was added in small portions over a period of 0.5 h. The mixture was stirred at -18°C for 0.5 h, warmed to room temperature, and refluxed for 3.5 h. The reaction was quenched by the addition of ice-water and the resulting solid was collected by filtration and dried. The solid was dissolved in methylene chloride and the insoluble inorganic material was removed by filtration.. The filtrate was evaporated and the residue was recrystallized from cyclohexene to give 7.73g (51%) of E-1,2-di-2-thienylethylene. mp 131-132 °C (lit.,[152] mp 133-134°C).

1,2-Bis-(thiophen-2-yl)-ethanol (419)

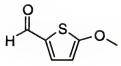


To a dissolved solution of alkene (0.184g, 0.93 mmol) in 10 ml of THF was added (0.28 g, .3.4 mmol) of BH_3THF complex at 0^oC. Solution was refluxed for 3hrs. 3 ml of H_20 followed by 3 ml of 3M aqueous NaOH and 3 ml of 30% H_2O_2 was added. The mixture was extracted with ether (3 x 15ml) washed with H_2O, brine, and dried with $MgSO_4$. Column Chromatography yielded 179 mg of a yellow oil, 50% yield. $R_f = 0.62$ hexanes:ethyl acetate 3:1; Bp = 183-185 ^oC at 13 Torr. (lit.[152] 187-189 ^oC at 13 Torr.); Proton spectra data matched the reported literature values.

2-Methoxythiophene (420)

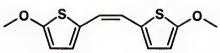
2-Iodothiophene (10g) and pulverized cupric oxide (2.3g) were added to a solution of sodium methoxide in absolute methyl alcohol (40g). the mixture was stirred and reluxed overnight. The cooled solution was then filtered, poured in tow volumes of cold water and extracted with ether. The solvent layer was washed with water, dried and evaporated. Distillation of the residue from sodium gave 3.9g (80%) of a colorless liquid. B.p. 76-77 °C (lit.[153] b.p. 74-75 °C). Proton spectra data matched the reported literature values.

5-Methylthiothiophene-2-carbaldehyde (400)



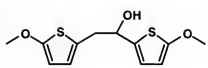
A solution of butyllithium (0.14 mol, 1.6 mol dm^{-3} solution in hexane, 86 ml) was added dropwise to a solution of 2-methoxy-thiophene (13.0 g, .0.11 mol) and TMEDA (14.0g, 0.12 mol) in anhydrous ether (200 ml) at 0°C. The resulting solution was stirred for 40 min at 0°C. Dimethylformamide (44.0g, 0.60 mol) was then added dropwise, and the solution stirred for 60 min at 0°C, and then acidified by the addition of aq. HCl (40 ml) The aq. layer was separated from the organic layer and extracted with ether (3 x 100 ml). The combined organic product solution was washed with brine (100 ml) and dried with MgSO4. After solvent removal the crude product was purified by flash chromatography, eluting with 30% ethyl acetate in hexane yielding **400** (13.0 g, 78%), m.p. 25-26 °C(lit.,[154] 24-26 °C). Proton values also matched to reported literature values.

1,2-Bis-(5-methoxy-thiophen-2-yl)-alkene (401)



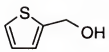
Anhydrous $TiCl_3$ (5.66g, 34.9 mmol) was stirred in 30 ml of dry DME under argon and Li pieces were added (.5g). After 1hr of reflux the mixture was cooled to room temperature and 2,5 methoxy-thiocarboxyaldehyde (.50g, 3.49 mmol) was added. Solution was brought back to reflux for 1 hr. 25ml of ether was added dropwise and the mixture was filtered through celite. Evaporation of solvent followed by recrystallization from ethanol gave a yellow solid (1.22g) in 70% yield (very unstable compound).. $R_f = 0.68$ hexanes:ethyl acetate 3:1; Mp = 112-113 °C; IR ($CHCl_3$) 1552, 1503, 1197, 1043, 77.1 cm^{-1};^1H ($CDCl_3$, 300 MHz) δ 6.57 (m, 4H), 6.05 (d, J = 3.6 Hz, 2H), 3.87 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 164.7, 129.5, 123.6, 119.4, 103.9, 60.0; HRMS calcd. for $C_{12}H_{12}O_2S_2$ $(M)^+$: 252.027; Found 252.028; Anal. Calcd. for $C_{12}H_{12}O_2S_2$: C, 57.12; H, 4.79. Found C, 57.27, H, 4.83.

1,2-Bis-(5-methoxy-thiophen-2-yl)-ethanol (421)



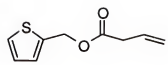
To a dissolved solution of alkene (0.90g, 3.4 mmol) in 10 ml of THF was added (0.28 g, 3.4 mmol) of BH_3·THF complex at 0°C. The solution was refluxed for 3hrs. 3 ml of H_20 followed by 3 ml of 3M aqueous NaOH and 3 ml of 30% H_20_2 was added. The mixture was extracted with ether (3 x 15ml), washed with H_2O, brine, and dried with $MgSO_4$. Column Chromatography yielded 460 mg of a yellow oil, 50% yield. R_f = 0.68 hexanes:ethyl acetate 3:1; Mp = 104-106 °C; IR ($CHCl_3$) 3419, 2943, 1563, 1431, 1208, 1151, 998, 772 cm^{-1};^{1}H ($CDCl_3$, 300 MHz) δ 6.57 (m J = 3,9 Hz, 1H), 6.46 (m,1H), 6.01 (m, 2H), 4.87 (t, J = 6.6, 6.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s,3H), 3.10-3.08 (m,2H), 2.32 (bs, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ165.9, 165.3, 132.5, 125.5, 123.7, 121.8, 103.1, 102.8, 71.2, 60.2, 60.1, 40.2. HRMS calcd. for $C_{12}H_{14}O_3S_2$ $(M)^+$: 270.3716; Found 253.037; Anal. Calcd.: C, 53.31; H, 5.22. Found C, 55.51, H, 5.17.

thiophen-2-yl-ethanol (415)



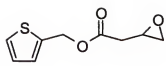
To a round bottom flask was added $NaBH_4$ and 10 ml of H_2O. The mixture was cooled to 0°C and the aldehyde (1g, 6.9 mmol) dissolved in 5 ml of THF was added dropwise. Upon the completion of the reaction, 3N NaOH was added and the mixture extracted with ether. The organic layer was washed with 10% aqueous NH_4OH, dried with $MgSO_4$ and evaporated. Flash chromatography gave a yellow oil (836 mg) in 84% yield. Bp.105-106 °C at 16 Torr. (lit.[154] 101-102 °C at 16 Torr.).

But-3-enoic acid thiophen-2-ylmethyl ester (416)



To a flame dried round bottom flask was added dry CH_2Cl_2 (20 ml) and vinyl acetic acid (583 mg, 6.0 mmol). The solution was cooled to 0°C with an ice bath and N,N-Dicyclohexylcarbodiimide (906 mg, 4.4 mmol) followed by Dimethylaminopyridine (catalytic amount) was added. A dissolved solution of the thioalcohol (516mg, 4.0 mmol) in CH_2Cl_2 was slowly added via a syringe and the mixture allowed to warm to room temperature and stirred for 18hrs. To the heterogeneous mixture was added SiO2, the solvent removed and flash chromatographed with 3:1 hexane:ethyl acetate. A yellow oil was recovered (691mg) in 84% yield. IR ($CHCl_3$) 1738, 1324, 1162, 992, 707 cm^{-1};^1H ($CDCl_3$, 300 MHz) δ 7.31 (d, J = 4.8 Hz, 1H), 7.09 (d, J = 3.3 Hz,1H), 6.97 (dd, J = 4.8, 3.6 Hz, 1H), 5.98-5.85 (m,1H), 5.27 (s, 2H), 5.14(m, 2H), 3.12 (d, J = 6.9 Hz, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ171.0, 137.6, 129.8, 128.1, 126.8, 126.7, 118.7, 60.6, 38. HRMS calcd. for $C_9H_{10}O_2S$ $(M)^+$: 182.0402; Found 182.0400; Anal. Calcd.: C, 59.32; H, 5.53.

Oxiranyl-acetic acid thiophen-2-yl methyl ester (417)

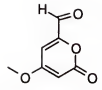


Vinyl acetic ester (532mg, 2.8mmol) was dissolved in CH_2Cl_2 and cooled to 0°C with an ice bath. To the solution was added *m*CPBA (1.47g, 8.5mmol), warmed to room temperature and allowed to stir for 18hrs. The reaction was monitored by TLC and upon completion, 10% $NaSO_4$ was added, followed by $NaHCO_3$, brine and the mixture was dried with $MgSO_4$. Removal of the solvent by in vacuo, followed by flash chromatography (3:1 hexane:ethyl acetate) afforded epoxide (10 mg) in 5% yield. IR ($CHCl_3$) 1733, 1407, 1322, 1171, 984, 708 cm^{-1};^1H ($CDCl_3$, 300 MHz) δ7.33 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 3.0 Hz,1H), 6.99 (dd, J = 4.8, 5.1 Hz, 1H), 5.31 (s, 2H), 3.30 (m, 1H), 2.85 (t, J = 4.2, 4.5 Hz, 1H), 2.59 (dd, J = 6.3, 3.3 Hz, 2H), 2.56 (dd, J = 4.5, 2.7 Hz, 2H).

4-Methoxy-6-methyl-2H-pyran-2-one (423)

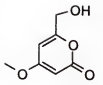
To a solution of hydroxypyrone **422** (7.3 g, 58 mmol) in DMF (290 mL) were added K_2CO_3 (16 g, 116 mmol) and methyl *p*-toluenesulfonate (22g, 166mmol) at 3 °C. The mixture was allowed to warm to ambient temperature. After 12 h of stirring, the mixture was poured into water and the aqueous layer was separated and extracted with CH2Cl2. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from EtOAc to afford methoxypyrone **423** (5.00g) as white crystals. The mother liquor was concentrated in vacuo and purified by silica gel flash chromatography ($CHCl_3$/acetone, 4:1) to give **423** (1.54 g, 79%) as white crystals; mp 88°C (from EtOAc), (lit.[155] 86-87.5 °C).

6-formyl-4-methoxy-2-pyrone (424)



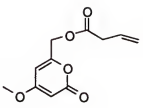
A mixture of the pyrone **423** (0.280g, 2 mmol) and selenium dioxide (1.10 g, 10 mmol) in anhydrous dioxane (8 ml) was heated at 180 °C in a sealed tube under vigorous stirring. After 1h, the precipitate was removed by filtrating and washed and dichloromethane/methanol (20:1). The combined filtrate and washings were concentrated to almost dryness. The residue was separated by silica gel chromatography using dichloromethane/methanol (20:1) as eluent. Aldehyde **424** was obtained as a off-white solid 199 g (65%), m.p. 175 °C (lit.[156] m.p. 177-178 °C).

6-hydroxymethyl-4-methoxy-2-pyrone (425)



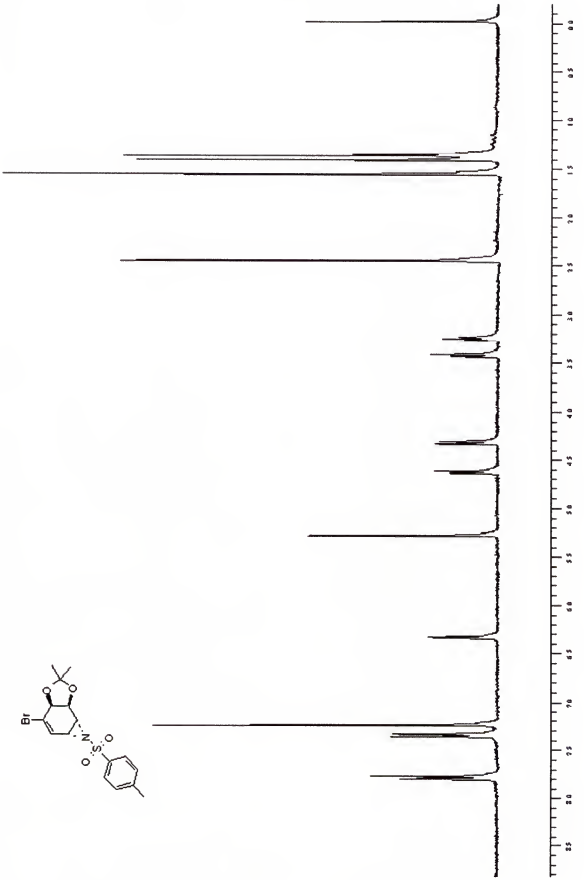
To a round bottom flask was added $NaBH_4$ and 10 ml of H_2O. The mixture was cooled to 0°C and the aldehyde **424** (1g, 6.9 mmol) dissolved in 5 ml of THF was added dropwise. Upon the completion of the reaction, via monitoring by TLC, 3N NaOH was added and the mixture extracted with ether. The organic layer was washed with 10% aqueous NH_4OH, dried with $MgSO_4$ and evaporated. Flash chromatography gave a white solid (836 mg) in 84% yield. Mp 177-179°C (lit.[157] 180-181 °C).

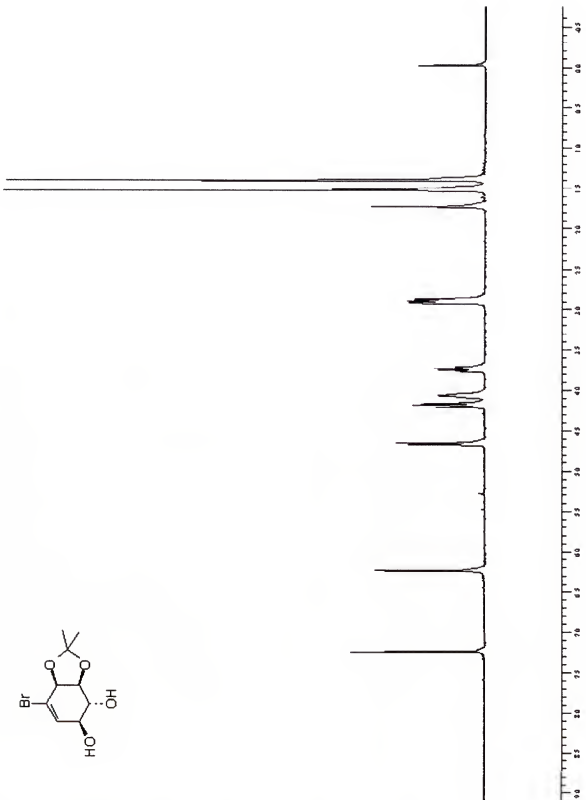
But-3-enoic acid 5-methoxy-2-oxo-2H-pyran-3-ylmethyl ester (426)

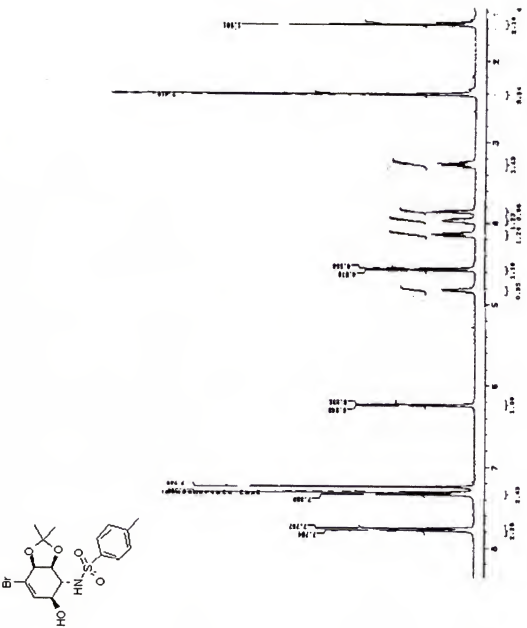


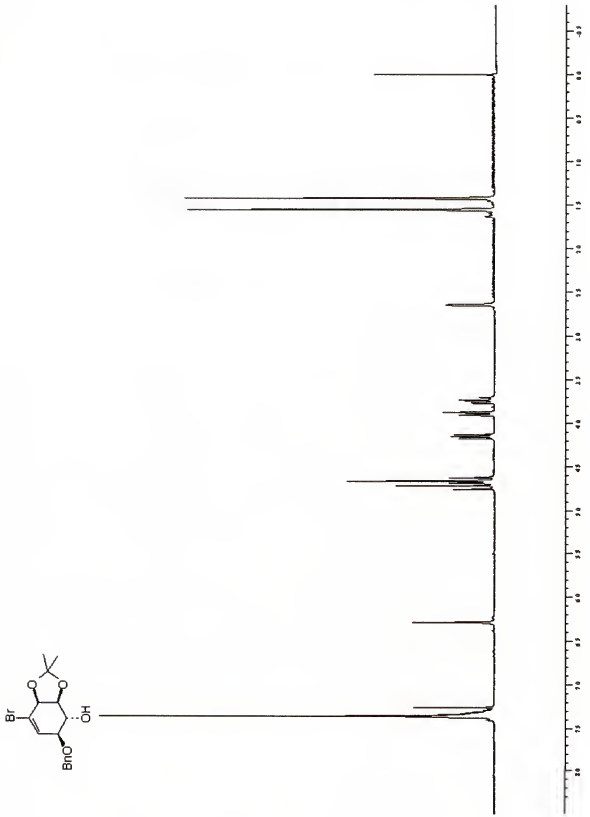
To a flame dried round bottom flask was added dry benzene (5 ml) and vinyl acetic acid (124 mg, 1.4 mmol). The solution was cooled to 0°C with an ice bath and a solution of 24 in benzene was added dropwise. To the mixture was added a catalytic amount of *p*-TsOH and the solution was refluxed in a Dean-Stark apparatus for 27 hrs. To the heterogeneous mixture was added SiO_2, the solvent removed and flash chromatographed with 3:1 hexane:ethyl acetate. A yellow oil was recovered and identified via nuclear magnetic resonance. IR ($CHCl_3$) 1732, 1659, 1573, 1251, 1143, 820 cm^{-1}; ^1H ($CDCl_3$, 300 MHz) δ 5.98 (s, 1H), 5.94-5.81 (m, 1H), 5.45 (d, J = 2.09 Hz, 1H), 5.21 (dd, J = 3.9 Hz, 2H), 4.82, (d, J = 3.6, 2H), 3.79, (s, 3H), 3.17, (dd, J = 5.4 Hz, 1.2 Hz, 2H).

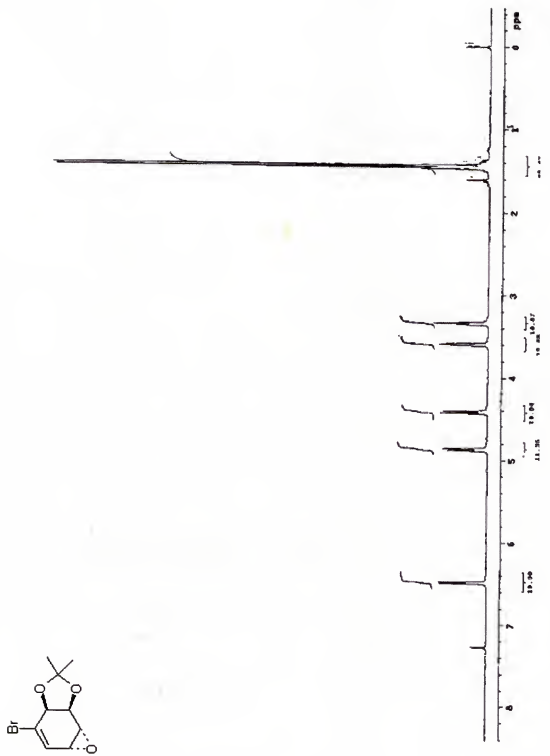
APPENDIX A
SELECTED SPECTRA

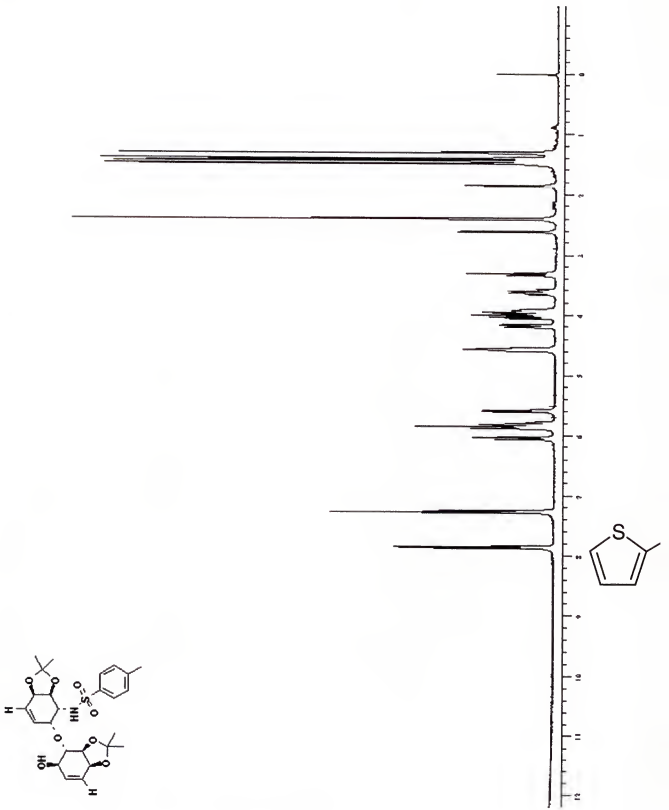

Br
N
S
O
O

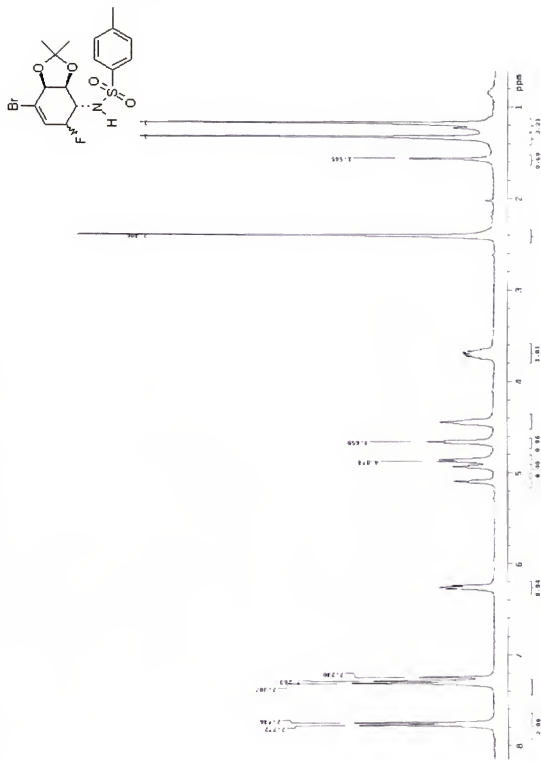

Br
OH
HO

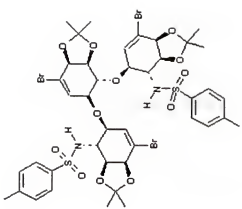

Br
HO
HN
S
O
O

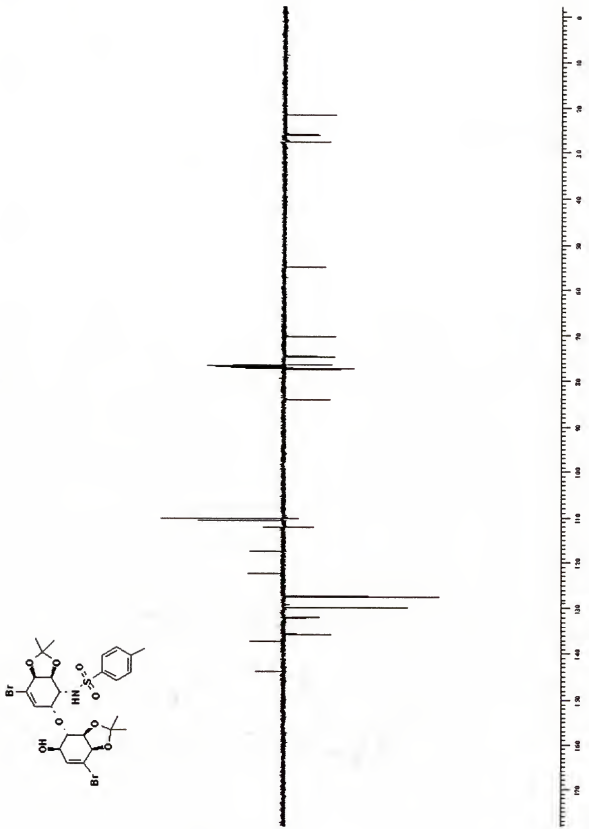

Br
OH
BnO

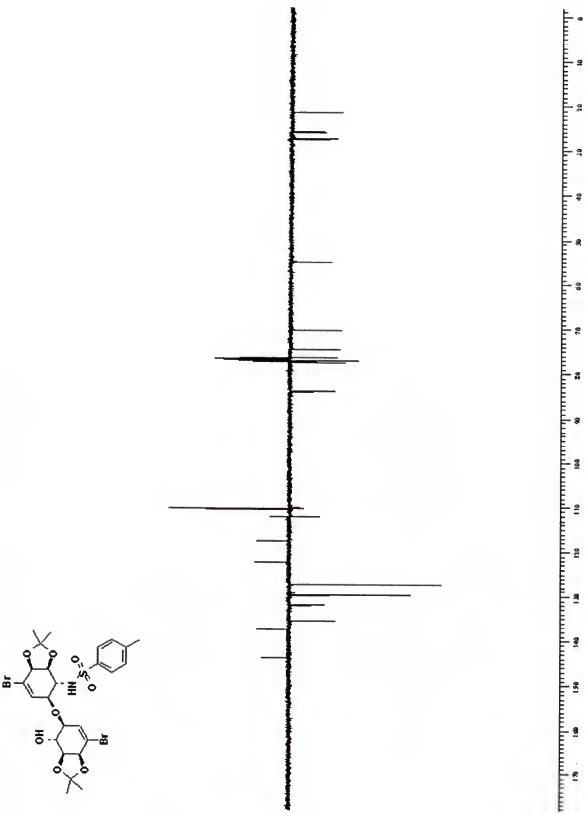

ppm
0
1
2
3
4
5
6
7
8
Br
O
O
O

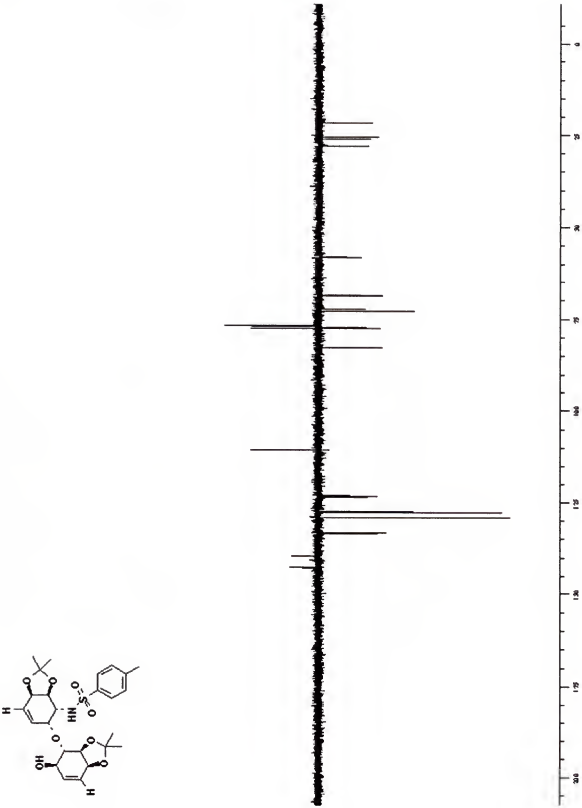


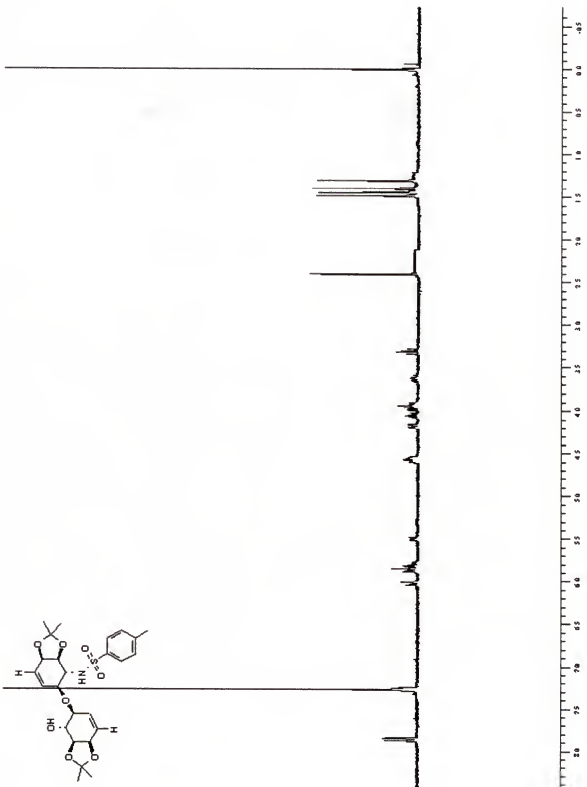

Br
O
O
O
O
S
O
O
N
H
F
7.744
7.270
7.263
7.180
7.288
6.659
6.474
3.565
2.000
1.000
0.994
1.013
2.913
ppm

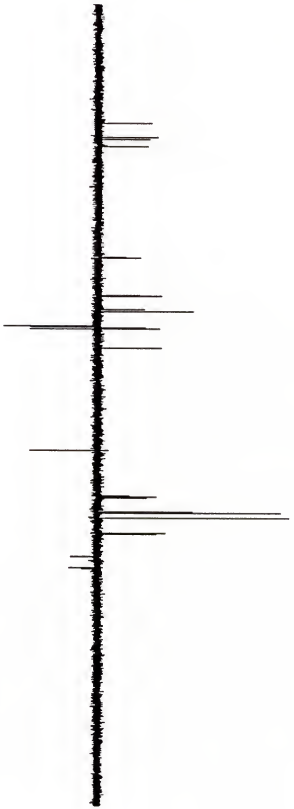


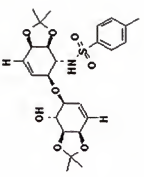

Br
O
O
HN
S
O
O
O
O
O
OH
Br

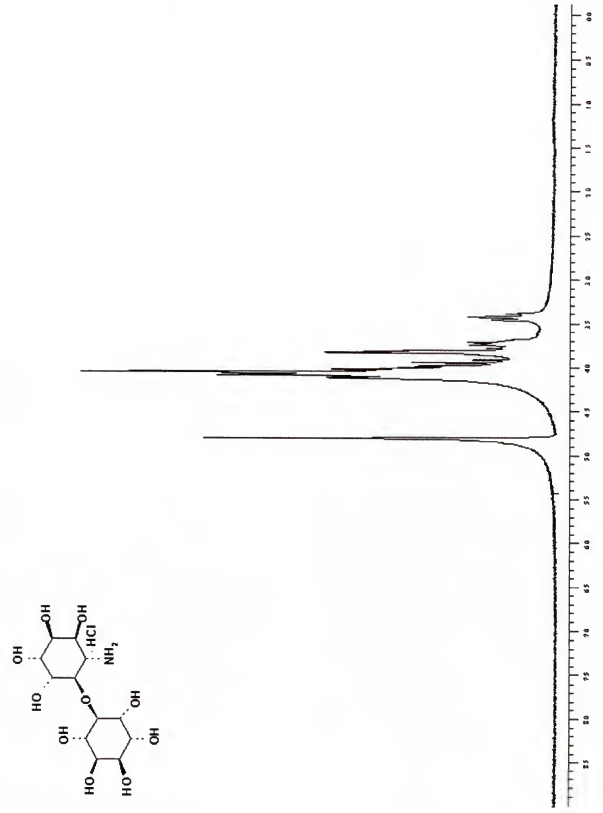

Br
HN
O
S
O
OH
Br
O
O
O
O



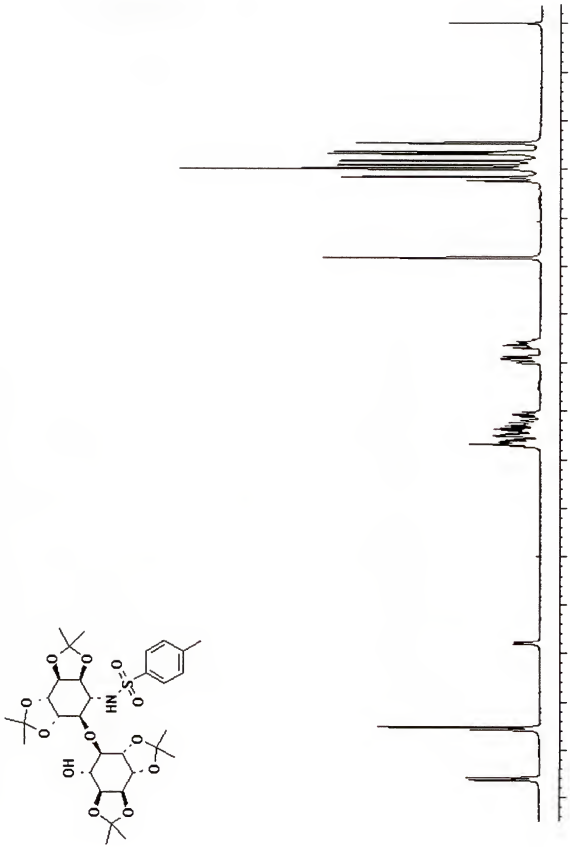


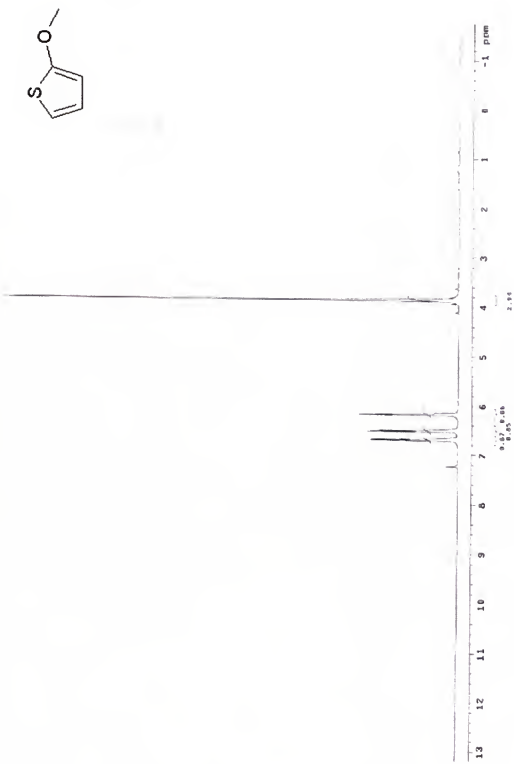

0
50
100
150
200
250
300

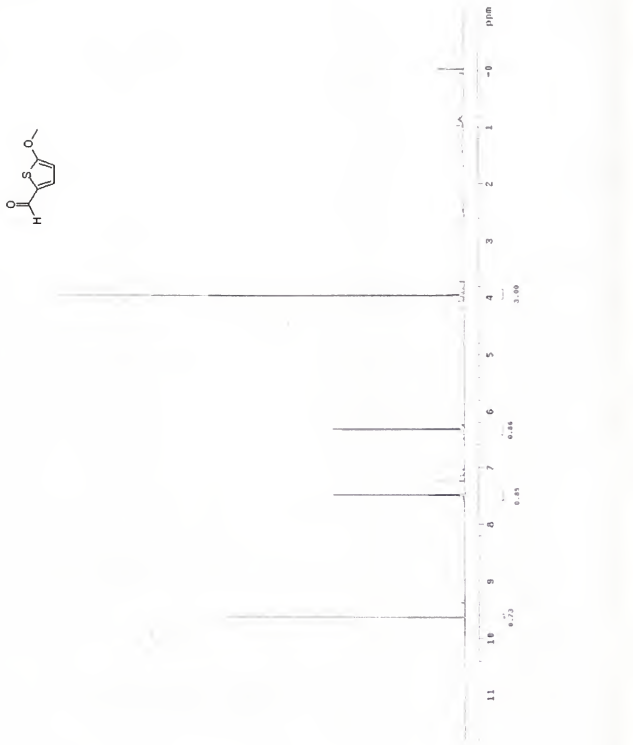

H
HN
O
S
O
O
OH
H

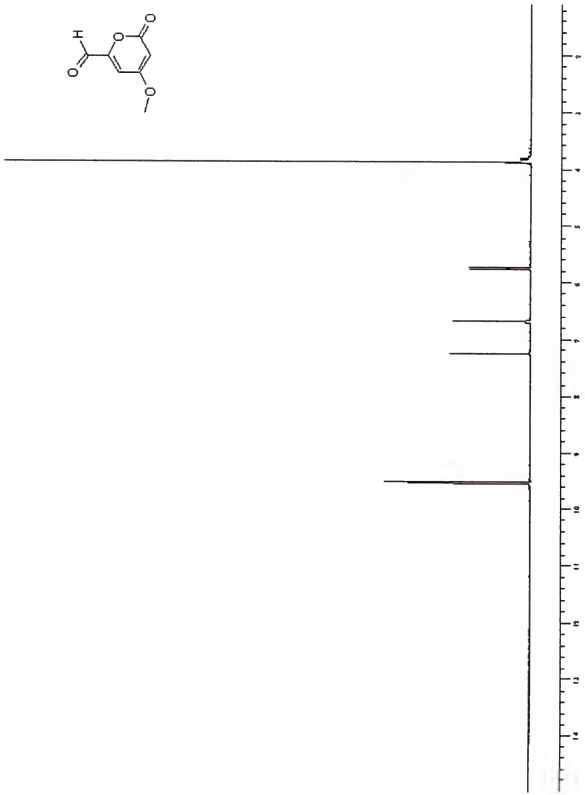

OH
OH
HCl
NH2
HO
O
OH
OH
OH
HO
HO

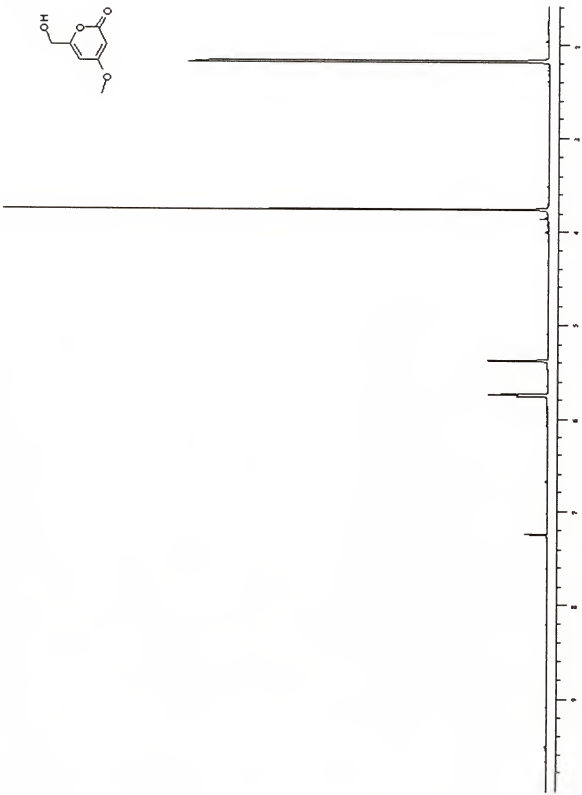
OH
OH
OH
NH2 HCl
HO
O
OH
OH
HO
HO

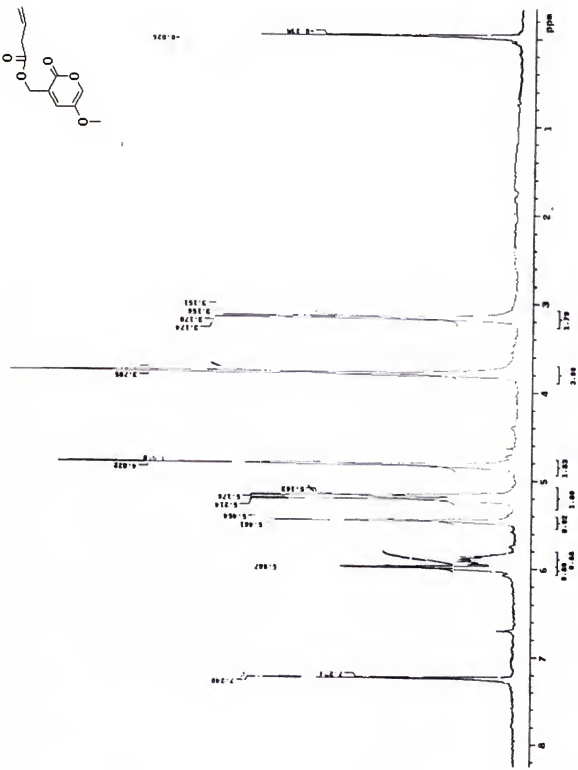


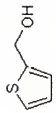

S
O
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.94
0.87
0.85

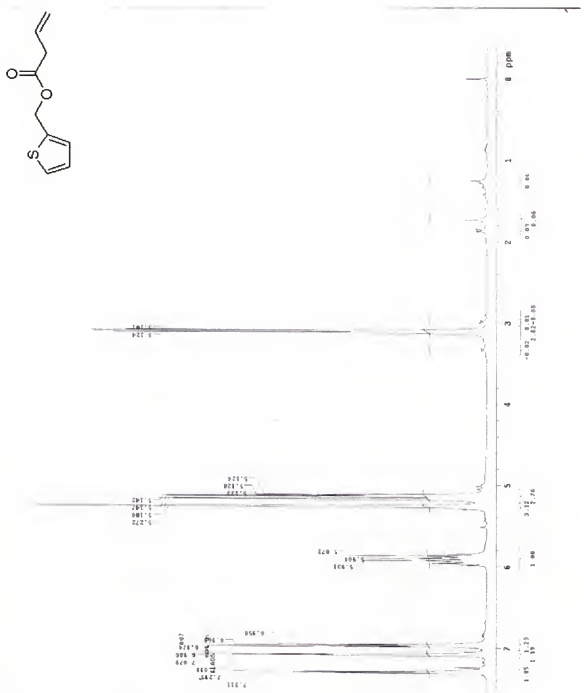

O
S
O
H
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.73
0.85
0.84
3.00

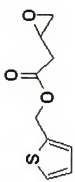


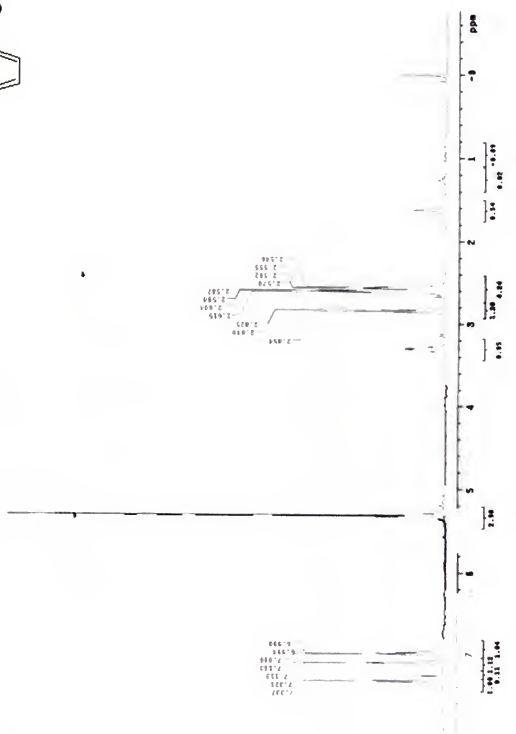


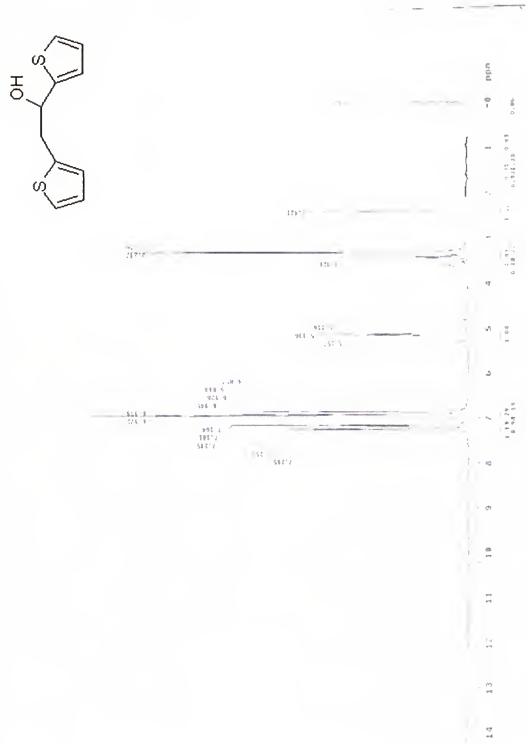



OH
S








OH
S
S
ppm

APPENDIX B
EXPERIMENTAL DATA

The following table contains all the experimental data obtained during the inhibition assays.

Table 4 Glycosidase inhibition of dimer **1** (O-I-D)

Enzyme		Sample Number				
		1	2	3	4	5
β-Galactosidase	Slope	0.02906	0.02572	0.01865	0.01451	0.01254
	Inhibitor concentration	0.000	0.375	0.750	1.125	1.500
	% Initial slope	100.0	88.5	64.2	49.9	43.2
β-Glucosidase	Slope	0.02035	0.01910	0.02445	0.02178	0.02042
	Inhibitor concentration	0.000	0.353	0.706	1.059	1.412
	% Initial slope	100.0	93.9	120.1	107.0	100.3
α-Mannosidase	Slope	0.03060	0.03239	0.03462	0.03324	0.03402
	Inhibitor concentration	0.000	0.353	0.706	1.059	1.412
	% Initial slope	100.0	105.8	113.1	108.6	111.2
α-Glucosidase	Slope	0.00915	0.00632	0.00523	0.00484	0.00459
	Inhibitor concentration	0.000	0.441	0.882	1.324	1.765
	% Initial slope	100.0	69.1	57.2	52.9	50.2
α-Galactosidase	Slope	0.03552	0.04004	0.03708	0.03686	0.03620
	Inhibitor concentration	0.000	0.419	0.838	1.257	1.676
	% Initial slope	100.0	112.7	104.4	103.8	101.9
β-Mannosidase	Slope	0.01152	0.01239	0.01077	0.01124	0.01122
	Inhibitor concentration	0.000	0.397	0.794	1.191	1.588
	% Initial slope	100.0	107.6	93.5	97.6	97.4

LIST OF REFERENCES

1. D. J. Ager, M. B. East, *Tetrahedron* **1993**, 5683.

2. C. S. Wilcox, J. J. Gaudino, *J. Am. Chem. Soc.* **1986**, 3102.

3. I. Miwa, H. Hara, J. Okuda, T. Suami, S. Ogawa, *Biochem. Int.* **1985**, 809.

4. A. B. Reizt (ed); *Inostiol Phosphates and Derivatives; Synthesis, Biochemistry and Theraputic Potential,* American Chemical Society, Washington, **1991**.

5. H. G. Fletcher Jr., *Adv. Carb. Chem. Biochem.* **1948**, 3, 45; S. J. Angyal, L. Anderson, *Adv. Carb. Chem. Biochem.* **1959**, 14, 135; L. Anderson in *Carbohydrate chemistry and biochemistry*, W. Pigman, D. Horton (ed.), Academic Press, **1972**, 519.

6. J. Scherer; *Ann.* **1850**, 322.

7. H. Wieland, R. S. Wishart; *Ber.* **1914,** 2082.

8. R. Kuhn, G. Quadbeck, E. Rohm, *Ann.* **1949**, 565.

9. L. Maquenne, *Compt. rend.* **1887**, 225, 297.

10. T. Posternak, *Compt. rend. soc. phys. hist. nat. Geneve* **1941**, 58, 44.

11. A. J. Kluyver, A. G. J. Boezaardt, *Rec. trav. chim.* **1939**, 956.

12. G. Dangschat, *Naturwissenchaften* **1942**, 146.

13. T. Posternak, *Helv. Chim. Acta* **1950**, 33, 1597.

14. J. Schubert, R. Keller, R. Schwesinger, H. Prinzbach, *Chem. Ber.* **1983**, 116, 2524.

15. T. Posternak, *Helv. Chim. Acta* **1936**, 19, 1007.

16. H. A. J. Carless, K. Busia, O.Z. Oak, *Synlett* **1992**, 672.

17. M. Mandel, T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1* **1993**, 741; also see M. Mandel, T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1537 [Erratum]; M. Mandel, T. Hudlicky, L. D. Kwart, G. M. Whited, *J. Org. Chem.* **1993**, 58, 2331.

18. J. L. Chiara, N. Valle, *Tetrahedron: Asymmetry* **1995**, 6, 1895.

19. Y. L. Merrer, A. Dureault, C. Greck, D. Micas-Languin, C. Gravier, J. C. Depezay, *Heterocycles* **1987**, 25, 541.

20. J. L. Chiara, M. Martin-Lomas, *Tetrahedron Lett.* **1994**, 35, 2969.

21. K. S. Kim, J. I. Park, H. K. Moon, H. Yi, *J. Chem. Soc., Chem. Commun.* **1998**, 1945.

22. S. K. Chung, Y. U. Kwon, *Bioog. Med. Chem. Lett.* **1999**, 9, 2135.

23. S. K. Chung, Y. Ryu, *Carbohydr. Res.* **1994**, 258, 145.

24. L. E. Brammer Jr., T. Hudlicky, *Tetrahedron: Asymmetry* **1998**, 9, 2011.

25. G. Dangschat, H. O. L. Fischer, *Naturwissenschaften* **1939**, 27, 756.

26. S. J. Angyal, P. T. Gilham, *J. Chem. Soc.* **1958**, 375.

27. C. R. Kowarski, S. Sarel, *J. Org. Chem.* **1973**, 38, 117.

28. H. A. J. Carless, K. Busia, O. Z. Oak, *Synlett* **1992**, 672.

29. T. Hudlicky, C. H. Boros, E. E. Boros, *Synthesis* **1992**, 174.

30. T. Hudlicky, L. E. Brammer, M. Desjardins, *Carbohydrate Research* **1997**, 39.

31. K. Chung, Y. T. Chang, *J. Chem. Soc., Chem. Commun.* **1995**, 11.

32. G. Mehta, S. Lakshminath, *Tetrahedron Lett.* **2000**, 41, 3509.

33. S. J. Angyal, N. K. Matheson, *J. Am. Chem. Soc.* **1955**, 77, 4343.

34. A. M. Riley, D. J. Jenkins, B. V. L. Potter, *Carbohydr. Res.* **1998**, 314, 277.

35. T. Hudlicky, N. Restrepo-Sanchez, P. D. Kary, L. M. Jaramillo-Gomez, *Carbohydrate Research* **2000**, 200.

36. G. Staedeler, F. T. Frerichs, *J. Prakt. Chem.* **1858**, 73, 48.

37. T. Posternak, *Compt.Rend. Soc. Phys. Hist. Nat. Geneve* **1941**, 58, 44; T.

Posternak, *Helv. Chim. Acta* **1942**, 25, 746; T. Posternak, *Helv. Chim. Acta* **1941**, 24, 1045.

38. R. C. Anderson, E. S. Wallis, *J. Am. Chem. Soc.* **1948**, 70, 2931.

39. B. Kohne, K. Praefcke, *Liebigs. Ann. Chem.* **1985**, 866.

40. A. J. Kluver, A. G. J. Boezaardt, *Rec. Trav. Chim. Pays-Bas.* **1939**, 58, 956.

41. C. Husson, L. Odier, Ph. J. A. Vottero, *Carbohydr. Res.* **1998**, 307, 163.

42. T. Posternak, *Helv. Chim. Acta* **1941**, 24, 1045.

43. T. Posternak, *Helv. Chim. Acta* **1946**, 29, 1991.

44. H. A. J. Carless, K. Busia, O.Z. Oak, *Synlett* **1992**, 672.

45. V. Pistara, P. L. Barilli, G. Catelani, A. Corsaro, F. D'Andrea, S. Fisichella, *Tetrahedron Lett.* **2000**, 41, 3253.

46. P. L. Barili, G. Berti, G. Catelani, F. D'Andrea, *Gazz. Chim. Ital.* **1992**, 122, 135.

47. R. C. Anderson, E. S. Wallis, *J. Am. Chem. Soc.* **1948**, 70, 2931.

48. S. J. Angyal, R. J. Hickman, *Carbohydr. Res.* **1971**, 20, 97.

49. S. J. Angyal, L. Odier, M. E. Tate, *Carbohydr. Res.* **1995**, 266, 143.

50. S. Ozaki, Y. Koga, L. Ling, Y. Watanabe, Y. Kimura, M. Hirata, *Bull. Chem. Soc. Jpn.* **1994**, 67, 1058.

51. S. J. Angyal, V. Bender, J. H. Curtin, *J. Chem. Soc.* **1966**, 798.

52. T. Suami, F. W. Lichtenthaler, S. Ogawa, *Bull. Chem. Soc. Jpn.* **1967**, 40, 1488.

53. T. Suami, S. Ogawa, *Bull. Chem. Soc. Jpn.* **1964**, 37, 1238.

54. S. J. Angyal, L. Odier, *Carbohydr. Res.* **1980**, 80, 203.

55. See ref. 29; T. Hudlicky, M. Mandel, J. Rouden, R. S. Lee, B. Bachmann, T. Dudding, K. J. Yost, J. S. Merola, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553.

56. T. Hudlicky, L. E. Brammer Jr., *Tetrahedron: Asymmetry* **1998**, 2011.

57. K. Kübler, *Arch. Pharm.* **1908**, 346, 320.

58. G. Dangschat, H. O. L. Fischer, *Naturwissenschaften* **1939**, 27, 756; G. Dangschat, H. O. L Fischer, *Carbohydr. Res.* **1987**, 164, 343.

59. M. Nakajima, I. Tomada, S. Takei, *Chem. Ber.* **1957**, 90, 246.

60. S. Knapp, R. M. Ornof, K. E. Rodriques, *J. Am. Chem. Soc.* **1983**, 105, 5494.

61. R. C. Cambie, N. D. Renner, P. S. Rutledge, P. D. Woodgate, *Synth. Coomun.* **1989**, 19, 537.

62. R. A. Aleksejezyk, G. A. Berchtold, *J. Am. Chem. Soc.* **1985**, 107.

63. Y. Sütbeyaz, H. Secen, M. Balci, *J. Chem. Soc., Chem. Commun.* **1988**, 133.

64. N. C. Yang, M. J. Chen, P. Chen. *J. Am. Chem. Soc.* **1984**, 106, 7310.

65. T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Andersen, J.D. Price, *Isr. J. Chem.* **1991**, 31, 229.

66. T. Hudlicky, H. Luna, *unpublished results.*

67. H. A. J. Carless, O.Z. Oak, *Tetrahedron Lett.* **1989**, 30, 1719.

68. D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhault, J. Espinal, S. Challal, *Bioorg. Med. Chem. Lett.* **1994**, 4, 2307.

69. K. L. Platt, F. Oesch, *Synthesis* **1977**, 7, 499.

70. H. B. Mereyala, B. R. Gaddam, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2187.

71. R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455.

72. Q. A. Mgani, A. J. H. Klunder, M. H. H. Nkunya, B. Zwanenburg, *Tetrahedron Lett.* **1995**, 36, 4661.

73. M. Honzumi, K. Hiroya, T. Taniguchi, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1999**, 1985.

74. L. Ackermann, D. E. Tom, A. Fürstner, *Tetrahedron* **2000**, 56, 2195.

75. S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, 115, 9858.

76. R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. Dimare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, 112, 3875.

77. H. Müller, *J. Chem. Soc.* **1907**, 91, 1790.

78. G. E. McCasland, E. C. Horswill, *J. Am. Chem. Soc.* **1953**, 75, 4020.

79. T. L. Nagabhushan, *Can. J. Chem.* **1970**, 48, 383.

80. S. J. Angyal, M. E. Tate, S. D. Gero, *J. Chem. Soc.* **1961**, 4116.

81. H. Paulsen, W. Röben, F. R. Heiker, *Chem. Ber.* **1981**, 114, 3242.

82. V. Calo, L. Lopez, A. Mineuzzi, G. Pesce, *Synthesis* **1976**, 200.

83. C. Le Drian, J-P. Vionnet, P. Vogel, *Helv. Chim. Acta.* **1990**, 73, 161.

84. T. Tsunoda, M. Suzuki, P. Noyori, *Tetrahedron Lett.* **1980**, 21, 1357.

85. T. Akiyama, H. Shima, S. Ozaki, *Tetrahedron Lett.* **1991**, 32, 5593.

86. T. Akiyama, N. Takechi, S. Ozaki, *Tetrahedron Lett.* **1990**, *31*, 1433.

87. J. E. Innes, P. J. Edwards, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1* **1997**, 795.

88. G. E. McCasland, J. M. Reeves, *J. Am. Chem. Soc.* **1955**, 77, 1812.

89. Y. K. Yurev, N. S. Zefirov, *Zh. Obshchei Khim* **1961**, 31, 685.

90. C. Le Drian, E. Vieira, P. Vogel, *Helv. Chim. Acta* **1989**, 72, 338.

91. H. A. J. Carless, O. Z. Oak, *J. Chem. Soc., Chem. Commun.* **1991**, 61.

92. H. Ziffer, D. M. Jerna, D. T. Gibson, V. M. Kobal, *J. Am. Chem. Soc.* **1973**, 95, 4048.

93. C. R. Johnson, P. A. Ple, J P. Adams, *J. Chem. Soc., Chem. Commun.* **1991**, 1006.

94. H. Secen, A. Maras, Y. Sütbeyaz, M. Balci, *Synth. Commun.* **1992**, 22, 2613; S. Takano, M. Moriya, Y. Higashi, K. Ogasawa, *J. Chem. Soc., Chem. Commun.* **1993**, 177; H. B. Mereyala, B. R. Gaddam, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2187; D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhault, J. Espinal, S. Challal, *Bioorg. Med. Chem. Lett.* **1994**, 4, 2307; H. Yoshizaki, J-E Bäckvall, *J. Org. Chem.* **1998**, 63, 9339; J-E. Bäckvall, *Pure Appl. Chem.* **1999**, 71, 1065.

95. T. Hudlicky, D. A. Frey, L. Koroniak, C. D. Claeboe, L. E. Brammer Jr. *Green Chemistry* **1999**, 57.

96. S. J. Angyal, P. T. Gilham, *J. Chem. Soc.* **1955**, 375.

97. R. Criegee, P. Becher, *Chem. Ber.* **1957**, 90, 2516.

98. H. A. J. Carless, O. Z. Oak, *Tetrahedron Lett.* **1989**, 30, 1719.

99. T. J. Donohoe, P. R. Moore, R. L. Beddoes, *J. Chem. Soc., Perkin Trans. 1* **1997**, 43.

100. T. J. Donohoe, P. R. Moore, M. J. Waring, N. J. Newcombe, *Tetrahedron Lett.* **1997**, 38, 5027.

101. M. Nakajima, I. Tomada, S. Takei, *Chem. Ber.* **1959**, 92, 163.

102. W.W. Lee, S. Chang, *Tetrahedron: Asymmetry* **1999**, 10, 4473; R. Angelaud, Y. Landais, *J. Org. Chem.* **1996**, 61, 5202; H. Secen, A. Maras, Y. Sütbeyaz, M.Balci, *Synth. Commun.* **1992**, 22, 2613; M. Honzumi, K. Hiroya, T. Taniguchi, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1999**, 1985; G. Mehta, S. Lakshminath, *Tetrahedron Lett.* **2000**, 41, 3505; S. Takano, T. Yoshimitsu, K. Ogasawara, *J. Org. Chem.* **1994**, 59, 54.

103. T. Hudlicky, J. D. Price, H. F. Olivo, *Synlett* **1991**, 645.

104. T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent, J. D. Price, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.

105. L. Dumortier, P. Lie, S. Dobbelaere, J. Van Der Eycken, M. Vanderwalle, *Synlett* **1992**, 243.

106. F. Chretien, R. Wolf, Y. Chapleur, *Nat. Prod. Lett.* **1993**, 2, 69.

107. V. Cere, F. Peri, S. Pollicino, *Tetrahedron Lett.* **1997**, 38, 7797.

108. V. Cere, G. Mantovani, F. Peri, S. Pollicino, A. Ricci, *Tetrahedron* **2000**, 56, 1225.

109. V. Plouvier, *C. r. hebd. Se Acad. Sci.* Paris **1962**, 225, 360.

110. H. Paulsen, W. Röben, F. R. Heiker, *Chem. Ber.* **1981**, 114, 3242.

111. H. Secen, Y. Sütebaz, M. Balci, *Tetrahedron Lett.* **1990**, 31,1323; L. Dumortier, P. Lie, S. Dobbelaere, J. Van Der Eycken, M. Vanderwalle, *Synlett* **1992**, 243; F. Chretien, R. Wolf, Y. Chapleur, *Nat. Prod. Lett.* **1993**, 2, 69; Q. A. Mgani, A. J. H. Klunder, M. H. H. Nkunya, B. Zwanenburg, *Tetrahedron Lett.* **1995**, 36, 4661; M. Honzumi, K. Hiroya, T. Taniguchi, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1999**, 1985; C. Le Drian, J-P. Vionnet, P. Vogel, *Helv. Chim. Acta.* **1990**, 73, 161; T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent, J. D. Price, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.

112. S. V. Ley, A. J. Redgrave, *Synlett* **1990**, 393.

113. T. Yoshimitsu, K. Ogasawara, *Synlett* **1995**, 257.

114. J. L. Chiara, N. Valle, *Tetrahedron: Asymmetry* **1995**, 6, 1895.

115. A. Patti, C. Sanfilippo, M. Piatelli, G. Nicolosi, *J. Org. Chem.* **1996**, 61, 6458.

116. N. A. Milas, S. Sussman, *J. Am. Chem. Soc.* **1936**, 58, 1302.

117. G. E. McCasland, S. Furuta, L. J. Durham, *J. Org. Chem.* **1966**, 31, 1516.

118. T. W. Millar, B. H. Arison, G. Albers-Schonberg, *Biotech and Bioeng* **1973**, 15, 1075.

119. Suami, T., *Topics in Current Chemistry* **1990**, 154, 257.

120. A. R. Saltiel, P. Cuatrecasas, *Proc. Natl. Acad. Sci. USA* **1986**, 83, 5793.

121. C. Murakata, T. Owawa, *Tetrahedron Lett.* **1990**, 31, 2439.

122. W. K. Berlin, S-N. Wang, T. Y. Shang, *Tetrahedron Lett.* **1990**, 31,1109.

123. W. K. Berlin, S. N. Wang, T. Y. Shang, *Tetrahedron Lett.* **1990**, 31,1109; R. Plourde, M. d'Alarcao, *Tetrahedron Lett.* **1990**, 31, 2693; S. V. Ley, L. L. Yeung, *Synlett* **1992**, 997; K. K. Reddy, J. R. Falck, J. Capdevila, *Tetrahedron Lett.* **1993**, 34, 7869.

124. D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhault, J. Espinal, S. Challal, *Bioorg. Med. Chem. Lett.* **1994**, 4, 2307.

125. M. Balci, *Pure and Appl. Chem.* **1997**, 69, 97; Y. Kara, M. Balci, S. A. Bourne, W. H. Watson, *Tetrahedron Lett.* **1994**, 35, 3349.

126. J. P. Michael, *Nat. Prod. Rep.* **1998**, 15, 571; J. R. Liddell, *Nat. Prod. Rep.* **1998**, 15, 363.

127. G. Mehta, D. S. Reddy, *Tetrahedron Lett.* **1999**, *40*, 9137.

128. G. Mehta, S.S. Ramesh, *Tetrahedron Lett.* **1999**, *40*, 991.

129. G. Mehta, S. S. Ramesh, *Tetrahedron Lett.* **2001**, *42*, 1987.

130. G. Mehta, D. S. Reddy, S. S. Ramesh, U. Tatu, *Tetrahedron Lett.* **1999**, 40, 9141.

131. M.A. Forman, W. P. Dailey, *J. Org. Chem.* **1993**, 58, 1501.

132. T. Hudlicky, A. J. Thorpe, *Synlett* **1994**, 899.

133. T. Hudlicky, K. A. Abboud, J. Bolonick, R. Maurya, M. L. Stanton, A. J. Thorpe, *J. Chem. Soc., Chem. Commun.* **1996**, 1717; T. Hudlicky, K. A. Abboud, D. A. Entwistle, R. Fan, R. Maurya, A. J. Thorpe, J. Bolonick, B. Myers, *Synthesis* **1996**, 897.

134. M. Desjardins, M. C. Lallemand, T. Hudlicky, K. A. Abboud, *Synlett* **1997**, 728.

135. L. M., Jones, R. H., Michell, *Biochem J.* **1975**, 148, 479.

136. M. R., Hokin, L. E., Hokin, *J. Biol. Chem.* **1953**, 203, 967.

137. M. J., Berridge, *Nature* **1993**, 361, 315.

138. G. Legler, *Adv. Carbohydr. Chem. Biochem.* **1990**, 48, 319.

139. D. T. Gibson, M. Hensley, H. Yoshioka, T. J. Mabry, *Biochemistry* **1970**, 9, 1626.

140. D. A., Evans, M. M. Faul, M. J. Bilodeau, *J. Org. Chem.* **1991**, 56, 6744.

141. All molecular modeling was performed with SPARTAN SGI version 5.1.1, available from Wavefunction Inc., on a Silicon Graphics O^2 workstation.

142. R. Saul, R. J. Molyneux, A. D. Elbein, *Arch. Biochem. Biophys.* **1984**, 230, 668.

143. Bernhard Paul, Synthesis , Structural and Biological Evaluation of Inositol Oligomers and Diaminoinositols, **2002**, University of Florida Ph. D. theisis dissertation.

144. A. H. Beckett, A. F. Casey, *J. Pharm. Pharmacol* **1954**, 986.

145. J. Nakayama, Y. Sugihara, *Topics in Current Chemistry* **1999**, 132.

146. E. Lukevics, P. Arsenyan, S. Delyakov, J. Popelis, O. Pudova, *Eur. J. Org. Chem.* **2002**, 3139; A. McKillop, D. Kemp, *Tetrahedron* **1989**, 3299; R. G. Hiskey, M. A. Harpold, *J. Am. Chem. Soc.* **1967**, 3191; R.P. Gajewski, J.L. Jackson, N.D. Jones, J.K. Swartzendruber, J.B. Deeter, *J. Org. Chem.* **1989**, 3311; B.M. Trost, D.P. Curran, *Tetrahedron* **1981**, 1287.

147. B. J., Paul, J. Willis, T. A. Martinot, I. Ghiviriga, K. A. Abboud, T. Hudlicky, *J. Am. Chem. Soc.* **2002**; 124, 10416.

148. C. Chen, C. Liao, *Organic Letters* **2000**, 2049.

149. T. Hudlicky, J. Price, F. Rulin, T. Tsunoda, *J. Am. Chem. Soc.* **1990**, 112, 9439; T. Hudlicky, J. D. Price, H. Luna, C. M Anderson, *Synlett* **1990**, 309.

150. T. Hudlicky, X. Tian, K. Konigsberger, R. Maurya, J. Rouden, B. Fan, *J. Am. Chem. Soc.* **1996**, 10752.

151. T. Hudlicky, L. Hector, H. F. Olivo, C. Anderson, T. Nugent, J.D. Price, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.

152. J. Nakayam, S. Murabayashi, M. Hoshino, *Heterocycles* **1986**, 2639.

153. J. Sice, *J. Am. Chem. Soc.* **1953**, 3697.

154. P. Emerson, *J. Org. Chem.* **1949**, 790.

155. H. Oikawa, T. Kobayashi, K. Katayama, Y Suzuki, A. Ichihara, *J. Org. Chem.* **1998**, 8748.

156. E. Suzuki, R. Hamajima, S. Inone, *Synthesis* **1975**, 192.

157. A. K. Ganguly, T. R. Govidachir, P. A. Mohamed, *Tetrahedron*, **1965**, 93.

BIOGRAPHICAL SKETCH

Jerremey Willis was born in Philadelphia, Mississippi on January 14, 1972. He is the son of Mr. Eddie Dave Willis and Ms. Marilyn Clayborne. As a youth he attended Philadelphia Elementary School. In 1984 he entered Philadelphia High School. There he became an honor student as well as an active member of DECA, Beta, and the varsity basketball team. He was also elected to several offices including junior class vice-president and senor class president. He obtained his high school diploma in 1990. and entered college as a Presidential scholar at Tougaloo College in August of the same year. In 1991, he became a member of Omega Psi Phi Fraternity Inc. and currently plays an active role in the membership process of his beloved fraternity. He is currently married to the lovely Mrs. Bethaney Michelle Willis and they are the proud parents of Cameron Matthew Willis and Courtney Michelle Willis.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky, Chair
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Dennis L. Wright
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Howard Johnson
Professor of Microbiology and
Cell Science

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

David E. Richardson
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle Battiste
Professor of Chemistry

This dissertation was submitted to the Graduate Faculty of the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 2002

_____

Dean, Graduate School